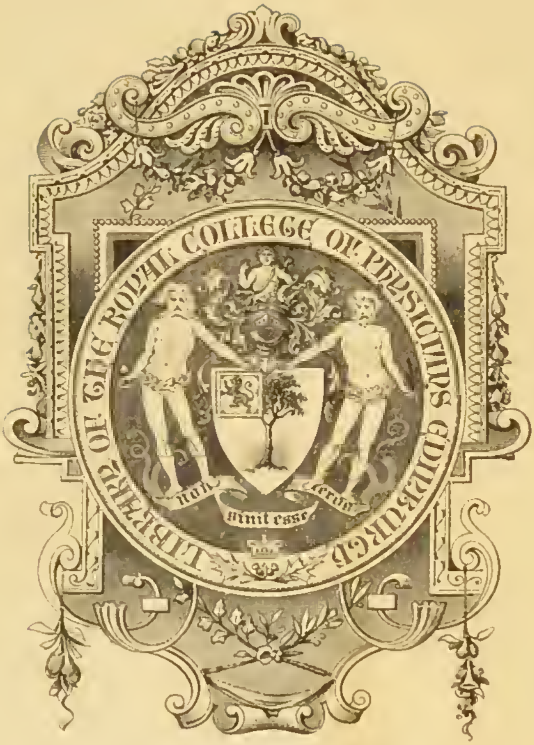
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SOME DISORDERS OF THE BLOOD AND BLOOD-FORMING ORGANS IN EARLY LIFE

The Goulstonian Lectures

ON

SOME DISORDERS OF THE BLOOD AND BLOOD-FORMING ORGANS IN EARLY LIFE

Delivered before the Royal College of Physicians of London
on March 8th, 10th, and 15th, 1904

BY

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The Goulstonian Lectures

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SOME DISORDERS OF THE BLOOD AND BLOOD-FORMING ORGANS IN EARLY LIFE.

LECTURE I.[1]

Mr. President and Gentlemen,—In no department, perhaps, of medical science has the progress of our knowledge been so rapid of recent years as in that which is concerned with the study of the blood and its disorders. Alike from a microscopical and from a chemical point of view great advances have been made and the march forward still goes on. Last year, it will be remembered, my predecessor in this lectureship gave to the College an able and exhaustive summary of one important branch of the subject—namely, the part played by the blood in the maintenance and production of immunity, and it may perhaps be felt that his successor would have done well to turn his attention to fresh fields and to new pastures. I venture to think, however, that in that corner of the field which I have selected for consideration—the disorders of the blood and blood-forming organs in early life—something still remains to be done. No one, I am sure, who sees much of disease in children can fail to feel how much obscurity still enshrouds many of these affections. Accordingly when I was honoured by an invitation to deliver the Goulstonian lectures for this year I felt that as one who has long been greatly interested in this subject and who has been fortunate in ample opportunity for its study I could not do better than take it as my theme even although I felt far from confident of my ability to throw any fresh light upon it. Without further apology then I propose to address myself to the task which lies before me.

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[1] Delivered on March 8th.

CHARACTERS OF THE BLOOD IN INFANCY.

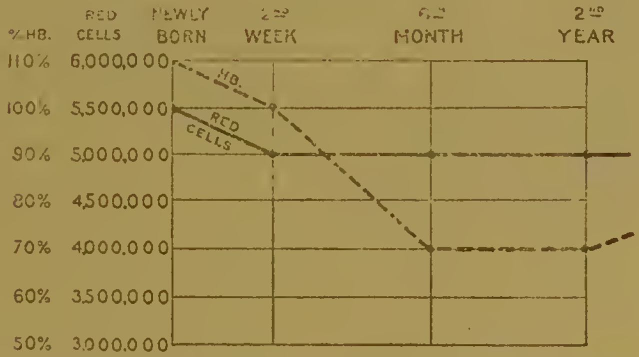
We can only hope to approach our subject in a satisfactory way by first glancing briefly at the characters of the blood and hæmopoietic organs in health during the first few years of existence. In doing so I must apologise if I describe facts which are already well known to an audience such as this, but a preliminary agreement upon some fundamental points regarding the development and histology of the blood and blood-forming organs is absolutely essential. In addition to this the study of blood formation in early life is worth making for its own sake, for it helps to throw light not only on the diseases of the blood met with in adult life but also on some of the fundamental problems of nutrition.

THE RED CORPUSCLES AND HÆMOGLOBIN.

The infant starts life with a number of red corpuscles considerably in excess of that met with in the adult, the average for the first day being about 5,500,000 per cubic millimetre. The appearance of this excess is a phenomenon of sudden occurrence, for the fœtal blood is not richer but poorer than the maternal in red cells up even to the very end of intra-uterine life The causes of this sudden enrichment of the blood on the entrance of the child into the world have been much discussed but do not materially concern us now. It may be said, however, in brief that there are probably several factors at work in its production, amongst which are : (1) a desiccation of the blood from loss of fluid by evaporation after birth ; (2) aspiration of blood out of the placenta by the first acts of respiration ; and (3), and perhaps most important of all, a sudden increase in activity of the blood-forming organs, an increase which coincides with a general increase of metabolism and which is rendered necessary by the demand for a larger supply of oxygen which the change from pre-natal to post-natal life entails. The marked excess of red cells is, however, not of long continuance. Very quickly it passes off, partly, it would seem, in consequence of an active destruction of red cells, partly from dilution of the blood which ensues upon the taking of liquid nourishment, and by the second week the adult figure of 5,000,000 per cubic millimetre is reached and persists with remarkable uniformity throughout the rest of life. The percentage of hæmoglobin at birth is in proportion to the great richness of the blood in red cells and amounts on an average to 110 per cent. Some observers even go so far as to say that the "worth" of each corpuscle is higher at birth than at any subsequent period. Richness in hæmoglobin is a characteristic even of the fœtal blood, each corpuscle in the fœtus containing a quarter more hæmoglobin than a maternal corpuscle (Cohnstein and Zuntz). It falls rapidly in the first week proportionally to the fall in the red cells and mainly from destruction of the latter.

The products of destruction of the excess of hæmoglobin have probably much to do with the production of that familiar condition, icterus neonatorum. The bile, as is well known, is the vehicle for the excretion of broken-down blood and when the latter is suddenly liberated in large amount, as it is during the first week of life, the viscidity of the bile may be so much increased in consequence that it stagnates in the ducts and being in part re-absorbed gives rise to icterus. It seems not improbable, however, that the whole of this hæmoglobin is not wasted but that the iron contained in it is stored up in the liver and made use of again in the formation of new blood pigment. Up to the second week of life the number of red cells and the percentage of hæmoglobin run parallel but after that time this parallelism ceases. Whilst the red cells continue, as we have seen, fairly stationary the percentage of hæmoglobin continues steadily to fall and reaches a minimum of 70 per cent. after the sixth month of life. (See Chart 1) This low figure persists throughout the whole of infancy and it is only with the beginning of the second year that a gradual rise makes its appearance which persists until the adult standard is at last reached somewhere about the sixth year or even later. This comparative poverty in hæmoglobin is one of the most striking characteristics of the blood of the young child. The formation of blood pigment seems to lag behind that of red cells, so that the worth of each corpuscle is lower in the child than in the adult. The explanation of this is not quite clear. In part it may be due to a notable deficiency of iron in the diet of infancy, a point to which we shall return later, but it would be rash to assume that this is the whole explanation, for such an assumption implies that the blood in infancy is not perfectly adapted to its functions and that the marrow would form more hæmoglobin if it could. Such an explanation might

CHART 1.



Proportion of hæmoglobin and red corpuscles throughout infancy.

hold good for pathology but not for a condition of health. On the other hand, it is not unlikely that the disproportion between the red cells and hæmoglobin in infancy is an adaptation to facilitate oxidation. The child requires relatively more oxygen than the adult alike because of its rapid growth and because owing to its large surface it has to produce much heat, and it may well be that the rapid interchange of gases in the lungs is best met by having a moderate amount of hæmoglobin distributed in a large number of corpuscles and so insuring the exposure of an extensive surface to the air in the alveoli. The amount of hæmoglobin would thus be the index of the true blood-need of the child and the relatively large number of red cells a device to make that amount as serviceable as possible. At all events, whatever the true explanation may be, the comparatively chlorotic condition of the blood in infancy is a fact of the greatest importance in the study of the blood disorders of this period of life, for as we shall see later this physiological condition may readily become exaggerated in states of disease.

The histology of the red cells in childhood need not detain us long. It is stated by many writers that they differ from those of the adult in exhibiting a tendency to inequality of size, which need not surprise us when we remember that they are probably being "minted" at enormously high speed, but such inequalities are probably of little significance. More striking is the appearance of nucleated corpuscles in the blood of the infant during the first few days of life. These are no doubt survivors of corpuscles which have been born in utero, but their complete disappearance within the first three days of life—after which they are usually no longer present—testifies to the extremely rapid blood destruction which is going on at this time.

One quality of the red cells remains to be discussed and that is their power of resistance to unfavourable conditions: in a word, are the red cells of the child more vulnerable than those of the adult? This is a question of which so far as I am aware no experimental solution has yet been attempted but it is well worthy of consideration. When we come to the study of the secondary anæmias of infancy I shall have occasion to bring forward pathological evidence in favour of the view that this greater vulnerability has an existence in fact, and if it be so it is probably to be explained by the more rapid formation of red cells in the child; a rapidity of formation which leads to their being turned out into the blood half fledged, as it were, and less capable of resisting destructive influences.

PLACE OF ORIGIN OF THE RED CELLS.

There are two stages of red blood formation during intra-uterine life: (1) an embryonic stage in which the blood-vessels and perhaps also the liver are the sites of formation; and (2) the fœtal stage proper in which red cells are formed in the liver, spleen, and bone marrow. These two stages pass into one another about the fourth month of intra-uterine life but as development goes on a process of specialisation of function takes place in which the bone marrow gradually becomes the sole site of formation. This stage is reached by the time birth takes place and I have certainly not been able to find any evidence either from my own observations or those of others that the liver and spleen take any active share in blood formation after extra-uterine existence has begun. This specialisation of function, however, is, in the case of the child, an arrangement of such recent establishment that it is easy, whenever a greatly increased demand for red cells occurs, for the monopoly of the marrow to be overthrown and for the liver and spleen again to take an active share in blood formation. Many writers believe, as a matter of fact, that this is a frequent occurrence in cases of profound anæmia in childhood. In the adult, as is well known, the territory of marrow given up to the formation of red cells is strictly limited and occupies besides the whole of the flat or spongy bones only the ends of the long bones. In the child, however, the area of the red marrow is much more extensive. Appearing at the centre of the diaphysis of the long bones about the end of the sixth month of intra-uterine life the red marrow spreads throughout the whole bone and for the whole period of infancy the entire shaft is filled with it. Gradually as growth goes on and as the primary cancellous tissue gives place to the permanent medullary cavity fat begins to make its appearance, but up to the period of puberty—in fact, until the growth of the bones is nearly completed—a considerable amount of red marrow is still present.

The wide extent of the red marrow in childhood is noteworthy for more reasons than one. In the first place it has a practical bearing on the morbid anatomy of the diseases of the blood at this time of life. For if one finds the whole shaft of a long bone occupied by red marrow one must not conclude, as one would be justified in doing in the case of an adult, that there has been during life an increased formation of red cells going on. That is so obvious as perhaps hardly to need to be pointed out. In the second place, it has an important physiological meaning, for if the whole of the marrow of the long bones in childhood is already occupied in the manufacture of red corpuscles there can be no reserve power of formation as there is in the adult. In the mature bones there is a large space normally filled with fat upon which the red marrow can encroach when there is any demand for a more rapid formation of red corpuscles. This takes place conspicuously in pernicious anæmia in which, as is well known, the whole of the shafts of the long bones may become filled with red marrow. But this cannot happen in the young child who, in consequence, must live more up to the limits of his blood-forming capacity. This may perhaps explain why children stand hæmorrhage badly and why it is that they are very apt to become anæmic on slight provocation. To this point we shall return in considering the secondary anæmias.

THE LEUCOCYTES.

In considering the number and variety of white cells met with in the blood of infancy it will be necessary for the sake of clearness to begin with their histological classification. Following the plan first introduced by Ehrlich and now generally adopted we can divide the white cells into the two great divisions of granular and non-granular. The first of these divisions includes the polynuclear neutrophile and eosinophile leucocytes, the characteristics of which in the child are exactly the same as in the adult and are too well known to need any description here. It is when we come to the second division that complications begin to creep in. There is no greater desideratum in hæmatology at the present moment than for some common agreement to be arrived at in the nomenclature of the non-granular white cells. One gets hopelessly confused in reading the literature of the subject to find the same cell described under several different names or the same name applied to several different cells. We badly need more light here and to have our ideas clarified as to the mutual relations of the different cells belonging to this class. Meanwhile it is the duty of everyone who writes on the subject to define clearly the meaning of the terms which he intends to employ. I propose throughout these lectures to adopt the following classification of the non-granular cells of the blood :—

1. *Lymphocytes*, meaning cells about the size of, or rather smaller than, a red corpuscle with a deeply staining nucleus which occupies nearly the whole of the cell and only a small margin of feebly basophile non-granular protoplasm.

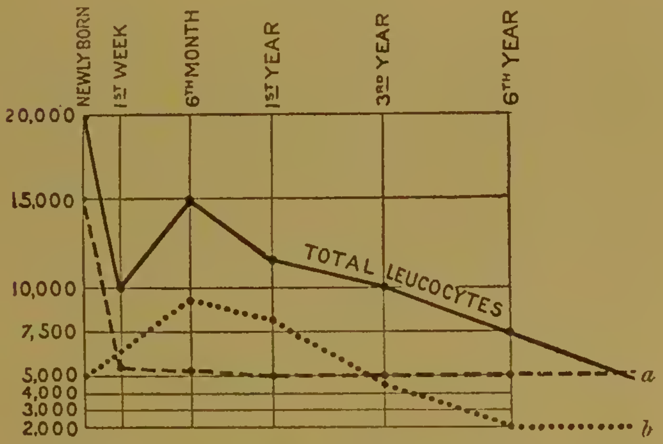
2. *Large lymphocytes*, being cells larger in size than a red corpuscle, with a nucleus which stains more diffusely than in the ordinary lymphocyte and a small ring of basophile protoplasm. These cells are not found normally in the blood of the adult but I believe that they are always present though in small number in infancy. All stages can be recognised between small and large lymphocytes. The large lymphocyte is probably a less mature form than the small.

3. *Large mononuclears*, cells varying from 8 to 12 μ in diameter with a large round or oval nucleus which stains rather faintly and a relatively broad margin of clear protoplasm which stains only "greyish" with methylene blue.

4. *Transitionals*, which resemble the above except that the nucleus is deeply indented.

As regards their *character* it will be noticed that these cells are, with the exception of the large lymphocytes, identical with the white cells commonly met with in the blood of the adult. It is when we come to consider their numbers, however, that striking differences become manifest and here I should like to point out, as has already been done by Phear, that it is not sufficient to make merely a differential percentage count of the white cells in the blood, for one is then apt to get a totally erroneous idea of the true state of affairs. A high percentage of any one kind of cell due to an absolute increase of its numbers in the blood makes all the other cells appear relatively diminished, although in reality their absolute number may be unaffected. What we want, then, is the absolute numbers of the different kinds of white cell in the blood at different ages. In Chart 2 these numbers are graphically represented. It will be observed that in the newly born infant the total number· of leucocytes is greatly increased compared with that in the adult and amounts to about 20,000 per cubic millimetre. Further examination shows that this pronounced leucocytosis is due to a high absolute number of polynuclear cells. During the first week of life, however, this number rapidly declines, with the result that the total number of white cells falls to about one-half what it was just after birth. A second rise then sets in which persists till the sixth month but this rise is due to the appearance in the blood stream of an increased number of mononuclear cells, chiefly lymphocytes. After the sixth month the number of lymphocytes slowly declines, and with them the total number of white cells, until about the sixth

CHART 2.

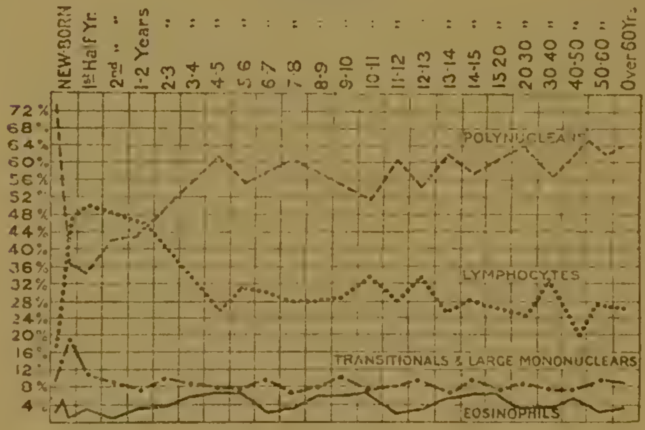


Absolute number of leucocytes per cubic millimetre at different ages.
a, Polynuclears. *b*, Lymphocytes.

year the figures characteristic of adult life are reached. Differential percentage counts bring out the same facts. (See Charts 3 and 4.)

To summarise, then, we have to deal with a polynuclear leucocytosis most marked just after birth and gradually falling off during the first week followed by a slow rise in the non-granular cells which reaches its maximum about the sixth month but which persists in a less pronounced form throughout the whole period of infancy. The granular cells reach by the end of the first week an absolute number (about 5000 per cubic millimetre) which they maintain unaltered throughout the whole of life, whilst the non-granular cells exhibit a gradual rise up to the sixth month and have declined by the end of the third year to a number equal to that of the granular cells and not till the sixth year have they reached a stationary point—viz., about 2000 per cubic millimetre—which persists into adult life. The broad and striking conclusions to be drawn from these figures is that the blood in infancy contains an absolute excess of white cells as compared with that of the adult but that this excess (after the first week) is due entirely to a surplus of one kind of cell only—viz., the non-granular cells (chiefly lymphocytes). The significance of the initial polynuclear leucocytosis is not understood. It is a phenomenon directly associated with birth, for the blood of the fœtus during the last month of gestation contains an absolutely smaller number of white cells than that of the mother and may perhaps be due in some obscure way to the total

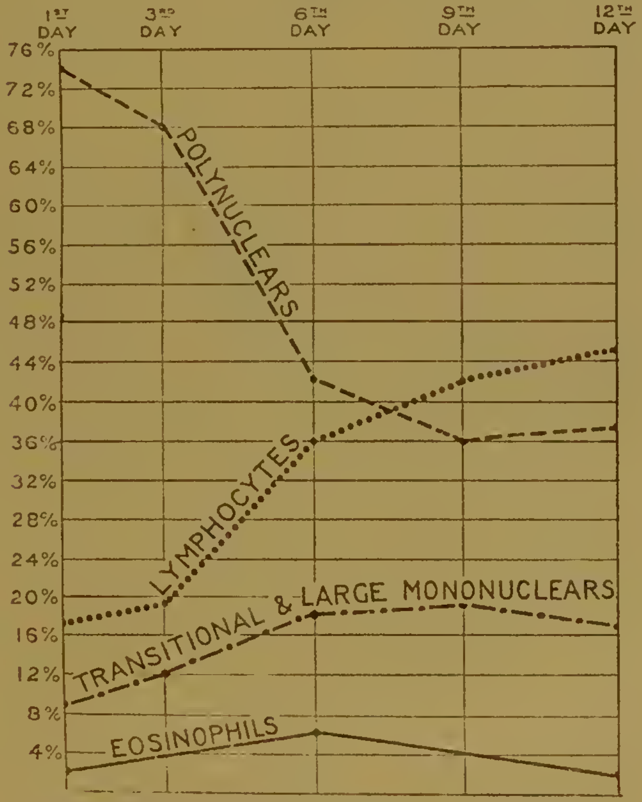
CHART 3.



Differential percentage counts throughout life. (After Carstanjen.)

change in metabolic conditions which birth entails. It coincides, too, with the period of active destruction of red cells already referred to and the polynuclears may perhaps be partly concerned in the removal of the débris of the latter from the circulation but that is a mere suggestion far removed from proof. The significance of the lymphocytic excess during infancy we shall be better able to appreciate when we have looked at the mode of production of the white cells as a class.

CHART 4.



Differential percentage counts during the first fortnight.
(After Carstanjen.)

SITE OF FORMATION AND MUTUAL RELATIONS OF WHITE CELLS.

Ehrlich, whose teaching on this matter has until recently been generally accepted, drew, as is well known, a sharp line of distinction between the granular and non-granular cells of the blood. He maintained the view that the former of these are derived entirely from the bone marrow and the latter from adenoid tissue, and that the two classes of cells were absolutely distinct and never passed into one another. Recently, however, a tendency has been shown, especially by Pappenheim, Wolff, Uskoff, and others, to deny the absolutely specific nature of the granular and non-granular cells and to trace them all back to one common parent cell from which even the red corpuscles are derived. This parent type—called by Wolff a "lymphoid" cell—is almost identical in character with the large lymphocyte and is the first to appear in the fœtal blood. From it in the opinion of Wolff, all the other cells of the blood are derived according to the following scheme :—

Lymphoid cell.

- Large lymphocyte.
  Small ,,
- Erythrocytes.
- Myelocytes :
  - (a) Basophile.
  - (b) Neutrophile.
    - Polynuclear leucocytes :
      - (α) With basophile granulation.
      - (β) ,, neutrophile ,,

In process of development a gradual differentiation of function takes place on the part of the blood-forming organs in consequence of which the lymphoid cells of the marrow confine themselves to the production of granular cells, whilst those of the adenoid tissue become exclusively concerned in the production of non-granular cells (lymphocytes). The specialisation, however, is never so complete but that when a demand for a greater number of cells of one type occurs the lymphoid cells in *any* blood-forming organ are able to produce that type. We shall recur to this point, however, when we come to study the leukæmias of childhood.

A study of the development of the marrow tends on the whole to confirm the above views. Up to the fourth month of intra-uterine life the marrow, according to the researches of Hammar, has merely the characters of a very vascular embryonic tissue full of branched spindle or star-shaped anastomosing cells imbedded in a homogeneous groundwork. About the beginning of the fourth month an infiltration of mononuclear leucocytes begins to appear about the middle of the diaphysis and gradually extends throughout the whole length of the bone so that at this stage the marrow has a lymphoid character. From these cells the ordinary myelocytes appear to be developed and can be detected in the marrow by the fifth month. By the time intra-uterine development is finished the histological differentiation of the marrow would appear to be as complete as in adult life, for although lymphoid cells of the type described by Wolff can be detected at all ages, they do not seem, so far as I have been able to observe, to be more numerous in infancy than in adult life. It is reasonable to suppose, however, that although in the child as in the adult the granular cells are derived exclusively from the marrow and the non-granular cells almost, if not quite, exclusively from adenoid tissue, yet the nearer the organism stands to the fœtus the more easily can a return to fœtal conditions take place and the lymphoid cells of the marrow assume vicariously the function of producing lymphocytes and those of the adenoid tissue that of producing granular cells. We shall have occasion to see that there is much pathological evidence in favour of the view that such vicarious function on the part of the two kinds of blood-forming organs actually takes place in many at least of the blood disorders of childhood.

ACTIVITY OF THE ADENOID TISSUE IN INFANCY.

If, then, the non-granular cells of the blood are derived in the child as in the adult mainly, if not entirely, from the adenoid tissue, the absolute excess of these cells which we have seen to be characteristic of the blood in infancy must indicate an unusual degree of activity on the part of the adenoid tissue throughout this period of life. I wish to emphasise this point as strongly as I can, for I believe it to be the key to the right understanding of many of the blood disorders of early life. From the physiological point of view we have to ask ourselves : What is the meaning of this activity of the adenoid tissue? It means, of course, that there is a greater demand for lymphocytes in the blood of the child than in that of the adult, but that simply brings us to the question, What is the function of the lymphocytes? To this question, as is well known, no definite reply has yet been afforded by physiology. We know that the lymphocytes play only a minor part, if any, in the defensive mechanism of the organism. There is no reason to believe that their rôle in this respect is of any greater import in the child than in the adult, for infectious disease is attended by a purely polynuclear leucocytosis at even the very earliest periods of life. On the other hand, it has been suggested, and a considerable amount of evidence has been adduced in favour of the view, that the lymphocytes play some part in nutrition, possibly by aiding in the absorption of food. It may be that this explains the greater demand for their services in the early years of life when nutrition is so active and when the normal diet contains relatively so much fat, a constituent in the absorption of which the lymphocytes are believed to take a particularly active share. Be this as it may, it is an undoubted fact that any condition of ill-health in infancy in which nutrition is impaired or rendered difficult tends to be accompanied by an exaggeration of the normal activity of adenoid tissue manifesting itself by an over development of the organs in which such tissue is most abundant, such as the thymus, spleen, and tonsils, and by the presence of an excess of lymphocytes in the blood. In normal circumstances the decline of lymphocytes in the blood coincides in time with the decline in the relative maximum activity of the thymus, but we shall see later that the lymphocytic character of the blood may sometimes persist beyond this period. Presumably in those cases the normal involution of the thymus is also delayed and such an occurrence is marked by delicacy of health. Pathologically the activity of the adenoid tissue is a fact of the greatest significance, for it is a well-recognised law in general pathology that the more active a tissue the more likely is it to become the seat of disease. Again and again one is struck with the fact, when viewing the blood disorders of infancy as a whole, that it is the affections of the adenoid tissue which dominate the picture; whilst in contrast to what is found in the adult, blood disorders in which the marrow is particularly involved are of rare occurrence. Thus pernicious anæmia and myelogenous leukæmia are almost unknown in early life, whilst changes in the adenoid tissue, whether in the form of local increase as in enlargement of the tonsils and the development of adenoids, or in the more grave forms exemplified by lymphadenoma, lymphatic leukæmia, and lymphosarcoma, are of comparatively frequent occurrence.

If I may gather these preliminary observations on the process of blood formation and its results in infancy to a focus I would say: 1. That the red marrow at this period of life is engaged almost to the limit of its functional capacity in the production of red cells; cells, however, which are individually less richly charged with hæmoglobin than those of the adult. 2. That the production of the granular forms of white cell goes on as in the adult in the marrow and apparently at almost the same rate of activity. 3. That the non-granular cells, on the other hand, are present in the blood of the infant in markedly larger absolute numbers than in the adult, and corresponding to this the adenoid tissue which is concerned in the production of these cells is extremely abundant, active, and widely diffused. 4. That although this specialisation of function on the part of the two great blood-forming tissues—the marrow and the adenoid tissue—has taken place in the child as in the adult, yet the former—standing nearer to the period of fœtal life—may be expected to be able under the stress of disease to revert more easily to the fœtal methods of blood formation and to exhibit in pathological conditions a less sharp degree of specialisation on the part of the marrow and adenoid tissue respectively. It is the combination of a high absolute number of non-granular cells with a relatively low percentage of hæmoglobin which constitutes the hall-mark of the infantile type of blood and in all conditions of profound anæmia in childhood these characters tend to assert themselves with even greater prominence. We are now in a position after this physiological preamble to turn to the study of the changes found in the blood and blood-forming organs in disease.

CLASSIFICATION.

The difficulty of constructing a satisfactory classification of anæmias has been felt by all writers on the subject. The difficulty is even greater when one is dealing with the blood disorders of early life than in the case of the adult owing mainly to the frequency of splenic enlargement from different causes in infancy and to the readiness with which a lymphocytosis develops in all conditions of lowered vitality at this time of life. Our ignorance of the actual cause of most blood disorders, moreover, is still too great to admit of any permanent grouping of the diseases which fall under this head. For descriptive purposes, therefore, we must content ourselves with a classification which is admittedly illogical, being founded partly on clinical and partly on pathological data. I propose, therefore, to divide the disorders of which I have to speak into the following great groups: (1) congenital abnormalities of the blood; (2) primary anæmias; (3) secondary anæmias; (4) blood disorders associated with enlargement of the spleen; (5) leukæmias; and (6) affections of adenoid tissue. We begin with:—

CONGENITAL ABNORMALITIES OF THE BLOOD.

That the blood, like any other tissue or organ, should sometimes exhibit congenital abnormalities or defects is not more than we would expect. We know, for instance, that in the condition called hæmophilia many people have postulated the existence of such a congenital abnormality. Such congenital defects would naturally fall into three divisions: (1) malformation of the blood considered as a tissue; (2) abnormalities in the total quantity of the blood or of some of its cellular constituents either in the direction of an excess or defect; and (3) abnormalities in the chemical composition of the blood. I shall deal only with the two former of these divisions, for as regards the third we are not yet in possession of sufficient data to make a consideration of it profitable.

1. *Congenital malformation of the blood* might reasonably be expected to occur as part of such congenital physical defects as affect the body as a whole. Examples of such malformation and mal-development at once rise to the mind as cretinism, Mongolism, and infantilism. The blood in cretinism has been examined by several observers without striking changes being found. Pollaci in two cases, aged seven and eight years respectively, found in one 7800 leucocytes, of which 60 per cent. were polynuclears, 25 per cent. lymphocytes, and 10 per cent. were transitional forms.

In the other case the polynuclears and small lymphocytes were both about 40 per cent., whilst there was 15 per cent. of large lymphocytes present. In three cases which I have examined from the point of view of the varieties of leucocytes present I found in one (aged one year) 43 per cent. of polynuclear and 57 per cent. of non-granular cells ; in another (aged three years) 30 per cent. of polynuclears and 69 per cent. of other cells ; and in a third (age nine years) 79 per cent. of polynuclears and 20 per cent. of non-granular forms. There is here, except in one instance (the second), no marked departure from the normal and in that case there was probably simple secondary anæmia present such as is met with in rickets. I know of no observations on the blood in Mongolism although the widespread malformation met with in that interesting condition might have been expected to draw attention to it. In a few well-marked cases which I have examined I found, however, no striking or characteristic change.

Turning to the third of the congenital malformations mentioned above—infantilism—one asks one's self : Does the blood in this condition preserve, like the body generally, its infantile condition ? I am aware that the term infantilism is one of rather indefinite significance and that it is difficult in particular to mark it off sharply from dwarfism on one hand and infantile myxœdema on the other. All the more on that account, however, is a study of the blood likely to prove of interest and seeing that it possesses throughout the infantile period of life such marked characteristics—characteristics already fully described—we possess in it a criterion for the maintenance or otherwise of a truly infantile state of body not easily to be found elsewhere. I have examined the blood in four cases which were believed to be examples of this condition in none of which was any general anæmia present and which had all reached an age far beyond that at which the blood normally assumes the adult characters.

The first of these, a girl, aged 17 years, who exhibited the physical and mental characteristics of a child of about half that age, showed the following differential count : polynuclears, 29 per cent. ; eosinophiles, 12 per cent. ; and non-granular cells, 59 per cent. The second, a boy, aged nine years, who exhibited physically and mentally great backwardness for his age, showed (total 8900) . polynuclears, 54·8 per cent. ; eosinophiles, 3·6 per cent. ; and non-granular cells, 41·6 per cent. The third, a girl, aged 18 years, who presented some features suggesting cretinism along with marked mental deficiency but who failed to respond to thyroid treatment, had in 6500 white cells per cubic millimetre, polynuclears, 66·1 per cent. ; eosinophiles, 7·7 per cent. ; and non-granular cells, 26·2 per cent. The fourth case was that of a girl, aged nine and a half years, who was brought because she was "not growing." Her height was only three and a half feet and her weight 2 stones 10½ pounds and physically she presented the characters of a child aged about five years. Her milk teeth were still present, the hair was rather coarse and dry, and her voice was deep and harsh but there were no signs of cretinism. She was childish and backward mentally but not in any sense imbecile. A blood film showed the presence of 60·4 per cent. of uninuclear, non-granular cells, and 39·6 per cent. of polynuclears.

It will be observed that in the first two and in the last of these cases the blood exhibited the marked excess of non-granular cells characteristic of infancy. In the third it was of the normal adult type. It may be that in the condition of the blood in these four cases we possess a means of classification and that whereas three of them should be regarded as purely infantile—i.e., in a state in which there is still the potentiality of growth—the third must be regarded as an example of development which is not so much arrested as proceeding on abnormal lines. We certainly want more information regarding possible delays in the assumption of the adult type of blood and their significance. Normally, as we have seen, this should happen somewhere between the third and sixth years but there is every reason to believe that the change is sometimes postponed until after that period. Roughly speaking, and so far as I have been able to observe, the feebler and more delicate the child the longer is the infantile type of blood maintained. On the side of the blood-forming organs this must correspond to a prolongation of the usual period of maximum activity of the adenoid tissue and there is reason to believe that such an occurrence is always an indication of delicate health and a feeble power of resistance but I shall return to this point when I come to speak of the condition known as "lymphatism."

2. *Congenital anæmias.*—Clinically, one meets from time to time with infants who have been markedly anæmic from birth. Putting aside those cases in which injudicious feeding, the repeated occurrence of diarrhœa and vomiting, or the existence of a syphilitic taint may reasonably be supposed to have induced an abnormal destruction of blood there remains a residuum of cases in which no such explanation is forthcoming. Such cases are, I admit, by no means common, but it must have fallen to the experience of everyone who sees much of disease in children to meet with them. The following are illustrative cases.

Case 1.—A boy, aged 15 months—an eight months child—of good family history, had been markedly pale since birth. The mother's health during her pregnancy was good and she never suffered from anæmia. The child was bottle-fed. He was well nourished but distinctly rickety and exhibited extreme pallor. Hæmic murmurs were present; the spleen was not enlarged. There were 3.213,000 red cells, 10.500 white cells, and 21 per cent. of hæmoglobin. The differential count showed 68 per cent. of lymphocytes, 29·5 per cent. of polynuclears, and 2 per cent. of eosinophiles. There was a considerable degree of poikilocytosis and one or two nucleated red cells were present. He ultimately improved greatly under the continuous administration of iron.

Case 2.—This patient was a girl, aged 13 months, a twin; the other twin was dead. There were four other healthy children, two of them twins. The state of the mother's health during pregnancy could not be ascertained. The child had been very pale since birth. She was slightly rickety and exhibited loud hæmic bruits but no enlargement of the spleen. The red cells numbered 1,776 000; the white cells 13.000; and the hæmoglobin was 12 per cent. There was considerable poikilocytosis. After persistent treatment for a year the hæmoglobin had only risen to 30 per cent. After this the child was lost sight of.

Case 3. A boy, one year old, born at the seventh month. There was one other healthy child in the family. Shortly after birth he was "deeply jaundiced" and on recovering from that was noticed to be very pale and was treated for anæmia by a medical man for several months. He was bottle-fed but had not suffered from diarrhœa or vomiting. Examination showed an extremely pale child with moderate rickets and a spleen which could just be felt. The blood contained 3,700,000 red cells, 3000 white cells, and 34 per cent. of hæmoglobin. He finally recovered under the persistent use of iron and laxatives.

Case 4.—A girl, aged two years, born at full time. The family history and mother's health were good. For six weeks after birth she was "orange coloured" and had been very pale ever since. She was fed on the breast for a year and afterwards on mixed diet. She had never had diarrhœa. She was an extremely pale child with a slightly yellowish tint. She had slight rickets; the spleen could not be felt. There were loud hæmic murmurs. The red cells numbered 1,920,000, the white cells 10,800, and the hæmoglobin was 28 per cent. A differential count showed 41 per cent. of polynuclears, 56 per cent. of mononuclears (mainly lymphocytes), 1 per cent. of eosinophiles, 1 per cent. of myelocytes, and 1 per cent. of mast cells. There were five normoblasts to every 100 white cells. The child subsequently developed some enlargement of the spleen.

It seems natural in such cases to try to connect the anæmia of the child with defective health on the part of the mother. Such an explanation, however, cannot always or indeed often be advanced. I have not found that the health of the mother during her pregnancy has been specially bad in such cases nor that she has herself suffered from anæmia. One has to remember, too, that the blood-forming functions of the fœtus are quite independent of those of the mother. This is certainly true at all events of the formation of blood cells. A striking illustration of it is found in the case of women suffering from myelogenous leukæmia who yet give birth to perfectly healthy infants. Of such an occurrence many cases are now on record and I have seen at least one well-marked instance of it myself. As regards the chemical constituents of the blood, however, it is by no means certain that such independence exists. Bunge has shown that the child comes into the world with a store of iron in the liver which is derived from the blood of the mother and serves as a supply of that metal throughout the earlier months of life. In some of the cases of congenital anæmia it would seem that this store is insufficient. This seems particularly apt to happen in the case of twins in which there is as it were not enough iron to go round and one twin or both suffers from a deficiency in consequence. In such a case the anæmia takes the form of a deficiency of hæmoglobin rather than of the red cells as a whole.

It is interesting to note that in two of the above cases the mother volunteered the statement that the appearance of the anæmia had been preceded by severe and prolonged jaundice, evidently an exaggerated degree of the ordinary icterus neonatorum. It may be that in such cases there has been an unusual amount of blood destruction, an amount which it has been beyond the power of the blood-forming organs fully to compensate or which has exhausted the available reserve of iron in the liver. When a defective supply of iron to the blood forming organs is the cause of the anæmia steady improvement follows the administration of iron by the mouth, but in other cases of anæmia dating from birth even the most persistent treatment with iron fails to effect any improvement. In such cases it is possible, though in the absence of more post-mortem evidence one does not wish to be too dogmatic about it, that there is a congenital defect in the red marrow and in consequence an insufficient formation of red cells. Muir[2] has recorded such deficiency of marrow coming on in a boy, aged 14 years, and attended by intense anæmia and there can be no *a priori* reason why it should not occasionally occur as a primary congenital defect In one fatal case of obstinate anæmia dating from birth I found that red cells and normoblasts were very scantily represented in the marrow which was mainly myeloblastic in type. In this case one could not resist the conclusion that the provision for the manufacture of red cells was defective.

Of an exactly opposite nature to such cases are those in which there is an excess of red corpuscles and of hæmoglobin in the blood, as is seen in *congenital cyanosis*. I do not propose to discuss the supposed reasons for the presence of a surplus of red cells in these cases but would merely point out that examination of them after death has shown an undue degree of activity on the part of the blood-forming organs and a persistence of the fœtal method of intra-capillary blood formation, especially in the thymus.[3]

PRIMARY ANÆMIAS.

1. *Chlorosis.*—If we define chlorosis as most authors seem inclined to do as a condition of anæmia exhibiting a marked relative deficiency of hæmoglobin but occurring only in young women then such a condition can have no place amongst the anæmias of infancy. There can be no doubt, however, that cases are met with in childhood which show at least a markedly chlorotic type of blood along with many of the other signs characteristic of the classical type of tho disease. The following are two typical examples.

CASE 1.—A girl, aged one year and seven months. She was a fat rickety child who got little animal food owing to the poverty of the parents. Her complexion was waxy. The spleen was just palpable; hæmic murmurs were present. The blood contained 4,000,000 red cells and only 20 per cent. of hæmoglobin. There was some poikilocytosis and a few normoblasts were present. Under treatment with iron the hæmoglobin rose in a month to 60 per cent.

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[2] A Case of Purpura and Intense Anæmia with Marked Deficiency in the Red Bone Marrow, Brit. Med. Jour., Sept. 29th, 1900.

[3] Weil: Note sur les Organes Hématopoiétiques et l'Hématopoièse dans la Cyanose Congénitale, Société de Biologie, June 29th, 1901.

CASE 2.—A girl, aged three years. She had been fed on the breast till 18 months old. Since then she had been rickety. Her complexion was chlorotic. Her spleen was palpable; hæmic murmurs were present. Red cells numbered 5,000,000, white 13,000, and hæmoglobin 31 per cent. The red cells were regular in size and shape. Under full diet and iron in large doses the hæmoglobin rose in six weeks to 62 per cent. and the child was discharged in good health.

It may be objected that these are simply examples of secondary anæmia associated with rickets. Such an objection I should not care to dispute. What I wish to emphasise, however, is that one does meet in infancy with anæmias characterised by blood of markedly chlorotic type associated with the greenish complexion, hæmic murmurs, and other well-recognised symptoms of the disease as it occurs in young women. Nor need such an occurrence surprise us. The blood of infancy is, as we have seen, normally poor in hæmoglobin compared with that of the adult and the presence of any factor which renders the formation of hæmoglobin still more difficult may readily lead to the appearance of a chlorotic form of anæmia. Such a factor is to be found, I believe, in a deficient supply of iron in the food. Human milk is at best but poor in iron, containing only from 3·5 to 7 milligrammes of the metal per litre (Friedjung[4]) and bad health in the mother may lower this proportion still further. The balance of iron required for purposes of blood formation is made up, as we have seen, from the store of it normally contained in the liver, but if the period of nursing—or of purely milk feeding—is unduly prolonged this reserve becomes exhausted and a deficiency in hæmoglobin results. Cases such as have been described seem specially apt to occur, therefore, amongst children who have been fed at the breast for a protracted period or who after weaning have been supplied with a diet in which animal food is but poorly represented. Such a diet is, of course, just such as is also apt to produce rickets and the correct view to take of such cases is, I believe, that the anæmia is not secondary to the rickets but that both the rickets and the anæmia are the common consequence of unsuitable food. For proof of this one would point to the striking improvements which such patients exhibit when put upon a diet rich in iron and especially when salts of iron are simultaneously given by the mouth.

2. *Pernicious anæmia.*—When we come to consider the question of pernicious anæmia in childhood we are again met by the difficulty of definition. I need not remind you how divided authorities are in this matter, some regarding the absence of any discoverable cause as the criterion of the disease, others basing its diagnosis upon the characters of the blood. These difficulties in the way of recognition of the disease, great as they are in the adult, are

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[4] Archiv für Kinderheilkunde, xxxii., p. 58, 1901. See also Fürst, Therapeutische Monatshefte, 9, 1900.

TABLE I.—RECORDED CASES OF PERNICIOUS ANÆMIA IN CHILDHOOD.

No.	Author and reference.	Sex and age.	General clinical characters.	Condition of the blood.	Result.
1*	Kjellberg (Archiv für Kinderheilkunde, v., p. 181; 1884).	M., 5 years.	Marked debility, lemon-yellow tint, hæmic mumurs, retinal hæmorrhages, and all the classical symptoms.	Red cells, 767,000, falling to 571,000; no further description.	Death in 16 weeks. Post-mortem examination was negative.
2	Steffen (Jahrbuch für Kinderheilkunde, xxviii., p. 444; 1888). Gives references to other cases of doubtful authenticity.	F., 16 months.	A rickety child, with general anæmia, but no splenic enlargement.	Red cells one-third of normal, pale but with no alteration of shape; white cells diminished.	Death. Post-mortem examination.
3	Escherich (Wiener Klinische 13 Wochenschrift, and 14; 1892. Contains references to previous alleged cases).	M., 4 years.	Extreme pallor; the spleen was not enlarged; there was some enlargement of the glands in the left side of the neck and left axilla.	Lowest red count 575,000; slight poikilocytosis; megalocytes, but no normoblasts; hæmoglobin from 12 to 15 per cent.; white cells diminished, lymphocytes predominating.	Death. No post-mortem examination.
4*	Mott (Practitioner, August, 1890).	M., 11 years.	Ill eight months; frequent vomiting; lemon-yellow tint; retinal hæmorrhages, &c.	Red cells, 800 000; hæmoglobin, 20 per cent.; marked poikilocytosis; micro- and macro-cytes; few normoblasts.	Death. Post-mortem examination showed typical appearances of pernicious anæmia.
5	Monti and Berggrüm (Die Chronische Anämie im Kindersalter, Leipsic, 1892).	M., 6½ months.	A pale, rickety child, with a history of congenital syphilis; the spleen was much enlarged.	Red cells, 868 000; hæmoglobin, 25 per cent.; white cells, 8400; marked poikilocytosis; numerous normoblasts and megaloblasts.	Death. No post-mortem examination.
6	Demme (quoted by Monti and Berggrüm, op. cit.).	M., 3 months.	Very anæmic since six weeks old; the spleen was not enlarged.	Red cells, 800,000; hæmoglobin from 28 to 30 per cent.; poikilocytosis; several megaloblasts.	Death. Post-mortem examination.
7	D'Espine and Picot (Revue de Medecine, 1890, p. 859).	F., 2 years.	Pronounced pallor and tendency to hæmorrhages coming on after previous good health; there was no enlargement of the glands or spleen.	Not examined.	Death after a month. No post-mortem examination, but the authors think that leukæmia could be excluded.
8	Ibid.	M., 13 years.	Gastro-intestinal symptoms (vomiting, diarrhœa, and colic) predominated; œdema of the limbs; the liver and spleen were not enlarged; there was frequent epistaxis.	,, ,,	Death. Post-mortem examination was negative.
9*	Theodor (Archiv für Kinderheilkunde xxviii.,	M., 11 years.	Ill for one year with all the typical symptoms and appear-	Red cells very pale; marked poikilocytosis; many megalocytes;	Death.

11*	Goodell (Scottish Medical and Surgical Journal, February, 1902).	M., 11 years.	Anæmia with hæmorrhages from the mucous membranes but none in the fundi; the spleen was not enlarged.	Red cells, 295,000; hæmoglobin, 5 per cent.; white cells, 20,000; four megaloblasts and 25 normoblasts to 1000 white cells.	Death. No post-mortem examination.

* The cases marked with an asterisk are probably genuine.

TABLE II.—CASES OF INFANTILE SCURVY TREATED WITHOUT ALTERATION OF DIET.

No.	Sex and age.	Symptoms.	Diet.	Treatment and result.
1	M., 9 months.	Sponginess of the gums and general tenderness of the bones.	Condensed milk and a tinned food.	Half an ounce of fresh orange juice daily. After a week the tenderness was diminished; the gums were as before; the diet was then changed.
2	F., 6 months.	Sponginess of the gums; thickening and tenderness of the lower end of the left femur and tibia.	Boiled milk, with a tinned farinaceous food.	Half an ounce of sterilised fruit juice daily. After a week all the symptoms were greatly improved; the diet was changed.
3	F., 10 months.	Sponginess of the gums; tenderness of the lower end of the left femur.	Condensed milk and Mellin's food.	Half an ounce of dialysed fruit juice daily. After a week the tenderness was very much less. There was still some sponginess of the gums; the diet was then changed.
4	M., 7 months.	Sponginess of the gums; thickening and tenderness of both femora.	Condensed milk and a tinned farinaceous food.	Half an ounce of dialysed lemon juice daily. After four days the sponginess of the gums had disappeared. The patient was then given 40 grains of citrate of potash daily. Four days later the tenderness of the legs was much less and the mother noticed "great improvement in every respect." The diet was then changed.
5	F., 8 months.	Moderate sponginess of the gums; the legs were tender but there was no thickening.	Condensed milk and a tinned food.	40 grains of calcium citrate daily produced no improvement in a week. After ten days' treatment with malate of potash the tenderness had almost gone and the sponginess was much less. The diet was then changed.
6	M., 8 months.	Sponginess of the gums; thickening and tenderness round the right knee.	Condensed milk and a malted food.	Citrate of potash in small doses produced no change after four days. The diet was then altered.
7	F., 12 months.	Sponginess of the gums and general tenderness.	Boiled milk.	Malate and tartrate of potash (10 grains of each daily). After a week all the symptoms had greatly improved. Raw milk was then given.
8	M., 11 months.	Considerable sponginess of the gums; tenderness but no swelling of the legs.	Condensed milk and nursery biscuits.	Malate of potash, 40 grains daily. As there was no improvement after four days ordinary treatment was begun.

greater still in the child. For at this time of life any secondary anæmia may take on a grave form marked by pronounced poverty of red cells, great variability in their size and shape, and the presence of numerous nucleated forms. The relative lymphocytosis, too, which is generally agreed to be a characteristic of the blood in pernicious anæmia is of little assistance in the diagnosis in infancy, during which, as we have seen, such a condition is of normal occurrence. Nor is it easy to recognise pernicious anæmia in infancy from its morbid anatomy, for one of its most striking pathological features—the replacement of the yellow marrow by blood-forming tissue—is found in the normal child. Evidences of increased blood destruction, such as the accumulation of iron in the liver, would be of more value, for, so far as I have seen, it is not found even in the severe secondary anæmias of childhood, but unfortunately this has not always been sought for in the reported cases. Whatever criterion we accept as identifying the disease it is generally admitted to be extremely rare in childhood. Rotch states that out of more than 2000 cases below the age of two admitted to the Infants' Hospital in Boston there was not one of true pernicious anæmia and I have searched the records of the Hospital for Sick Children, Great Ormond-street, for one in vain. In Table I. I have collected from all the available literature cases which have been published as examples of pernicious anæmia occurring in childhood.

It will be observed that they amount to not more than 11 in all, of which only five are at all probably genuine, and of these but one falls within the period of infancy. As in the adult, males appear to be much more frequently affected than females.

The rarity of pernicious anæmia in childhood is a surprising fact. Recollecting the vulnerability of the blood at this time of life and the ease with which injurious influences seem to affect it one would have expected, if pernicious anæmia be really due to the excessive destruction of blood by a poison, as most authorities seem to think, that it is at this time of life above all others that it would be most apt to occur. If, again, we have to deal in this disease with a resumption of the fœtal mode of blood formation with the appearance of megaloblasts in the blood or, at all events, in the marrow, as Ehrlich teaches, surely it is in the child who is but so little removed in time from the fœtal state that such a retrograde metamorphosis would be most prone to manifest itself. Nor are children exempt from those special destructive influences which have sometimes been invoked to explain the disease. Oral sepsis is a frequent and familiar condition in them and is believed by many to be a common cause of secondary anæmia; the parasitic anæmias also which may so closely simulate the genuine disease find striking illustration even in the earliest years of life (see cases of bothriocephalus anæmia published by Schapiro [5] and by Podwissotzky [6]). Whatever the explanation of the comparative immunity of young children to pernicious anæmia may be it is a striking fact in the natural history of the disease which must always be reckoned with in any attempt to account for its etiology.

SECONDARY ANÆMIAS

The characters of the blood and blood-forming organs in infancy are such as to render the young child peculiarly apt to become anæmic under the action of deleterious influences of various sorts. To this form of anæmia the term secondary or symptomatic anæmia may conveniently be applied. Such deleterious influences may act either upon the blood-forming organs, rendering them less capable of forming blood, or upon the blood itself leading to its increased destruction, or both modes of action may coexist. However produced, secondary anæmia in early childhood is apt to assume a severity rarely met with in adult life and in the most pronounced forms may present a blood picture which in the adult would justify a diagnosis of pernicious anæmia. One can distinguish, however, several grades of symptomatic anæmia. The hæmoglobin seems always to suffer first and in the mildest cases the blood has simply a slightly chlorotic character. This is not surprising when one remembers the fact, already insisted upon, that the infant's blood is normally poor in hæmoglobin and that the marrow seems only capable of forming it in limited amount. When the injurious influences are such as actually to destroy the red cells or seriously to impair the power of the marrow to form them the blood exhibits a poverty of red corpuscles in addition to a low percentage of hæmoglobin. In such circumstances irregular varieties of red cells (poikilocytosis) and nucleated forms very often make their appearance. It is the pronounced tendency for these abnormalities to develop which indeed specially distinguishes the secondary anæmias of infancy from those of adult life. Acting as it does even in normal conditions close up to the limit of its functional capacity and being unable, for reasons already mentioned, to increase its power of blood formation by a process of hyperplasia, the red marrow of the child when increased demands are made upon it for a greater production of red cells can only meet that demand by a more rapid division of its constituents instead of by extending the area of production over a wider territory. Such rapid production is apt to lead to imperfect formation of corpuscles and to their being turned into the blood stream in a "half-fledged" condition as it were, with their nuclei still present and with a feeble power of resistance. Hence it is that the presence of normoblasts and of poikilocytosis are such striking features in the secondary anæmias of childhood and the younger the child—i.e., the less the power of hyperplasia the marrow possesses—the more readily do such features make their appearance.

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[5] Wratsch, 1887.

[6] Jahrbuch für Kinderheilkunde, xxix., p. 223. See also abstract of another case (due to tænia) in Pediatrics, April 15th, 1896.

In the severest forms of secondary anæmia leucocytosis is apt to develop in addition to diminution of hæmoglobin and red cells. In many cases this is due to the presence of some complicating disease, of which perhaps broncho-pneumonia is in practice the most common. In such a case the leucocytosis assumes the ordinary polynuclear type. In some instances, on the other hand, and these especially in young infants, secondary anæmia is accompanied by an exaggeration of the normal excess of lymphocytes. I think, however, that the frequency with which this occurs has been overstated. Putting aside cases of severe rickets with splenic enlargement, to which we shall return in another lecture, it seems to be chiefly in anæmias associated with chronic gastro-intestinal disturbance that lymphocytosis is most apt to occur. One is tempted to suppose that there is here an over-production on the part of the adenoid tissue scattered throughout the abdominal tract, an exaggeration as it were of the normal digestive leucocytosis. If the lymphocytes in this situation are really normally concerned—as many people believe—in the absorption of food from the intestine it is not straining the imagination too far to suppose that any condition which renders difficult the process of absorption may be compensated by an over-production of these cells. Their increased numbers may enable as much as possible to be saved from the wreckage of food which is being swept on too fast into the lower bowel. The excess of lymphocytes in the blood in such a case would exactly correspond to the excess of red corpuscles met with in cases of cyanosis. In both instances over-production of the cell concerned is nature's way of overcoming obstacles in the way of its fulfilling its normal functions. But this, of course, is pure speculation.

It would be impossible to deal in any detail with the numerous injurious influences which may lead to the development of symptomatic anæmia, nor indeed would anything be gained by attempting to do so, but one or two typical illustrations may be selected. Of influences which probably act chiefly on the blood-forming organs malnutrition is one of the commonest and best marked. The most striking examples of the action of this influence which have come under my observation have been in the case of children who have been fed too long at the breast or who have been kept on a purely milk diet far beyond the time at which mixed feeding should be adopted. The following is a pronounced example of such a case.

A boy, aged two years and three months, a twin, born at the full time, had been feeble since birth. He had always been bottle-fed and when he came under observation was getting two quarts of milk a day without any other food. He exhibited extreme pallor without any sign of rickets and no enlargement of the spleen. There was a loud systolic murmur over the præcordia, the blood was very watery and contained 1,692.000 red cells, 4000 leucocytes, and 17½ per cent. of hæmoglobin. There were 60 normoblasts per cubic millimetre but no poikilocytosis. Under treatment with ordinary mixed diet and full doses of iron the number of red cells rapidly rose to 3,500,000 and the hæmoglobin to 43 per cent.

The special defects of the diet which are doubtless responsible for the production of the anæmia in these cases are: (1) poverty in iron; and (2) deficiency in proteid. The raw material for the production both of hæmoglobin and of red cells being thus lacking poverty of blood results. As both these defects are specially marked in a purely milk diet it is not to be wondered at that children who have been fed on such a diet too long should exhibit secondary anæmia in a striking form. To this point I have already referred in the discussion of chlorosis. There can be no doubt, too, that a similar cause is a potent factor in the production of milder degrees of anæmia in later childhood. Here is an illustration.

A girl, aged five years, had always been a pale child, but owing to the death of her mother had for some time been badly cared for and insufficiently fed. She was very chlorotic looking, had a just palpable spleen, and also loud hæmic murmurs. The blood contained 2,400,000 red cells, 15,000 white cells, and 40 per cent. of hæmoglobin. There was marked poikilocytosis but there were no nucleated red cells and of the white cells polynuclears predominated. She was put on a diet rich in animal constituents and full doses of iron and left hospital entirely cured.

I have selected here a pronounced example but such cases in a minor degree are met with every day. They are the peculiar product of poverty which necessitates the consumption of a diet which is not so much deficient in quantity as defective in quality, lacking especially those more expensive animal constituents which can alone insure a sufficient supply of proteid which is so essential in the building up of blood as of all tissues. Slight anæmia from this cause is a potent factor in the chronic ill health so often seen in the children of the working classes, particularly in large towns where the blood-forming functions are still further depressed by the absence of sunlight and fresh air. Nor should such slight degrees of anæmia be neglected, for although they may be, and usually are, fully recovered from later when a more generous diet is obtainable yet their effects may be irreparable. For it must not be forgotten that it is not a matter of indifference when the tissues and organs during the susceptible years of growth have been bathed with a poor and watery fluid instead of with rich and fruitful blood. Impairment of growth and development, shrinking of body and backwardness of mind, cannot fail to be the consequences and those to whom the present state of the national physique is a source of anxiety would do well, I believe, to look to this as a potent source of possible deterioration.

Of influences which lead to secondary anæmia by causing an increased destruction of blood the best examples are to be found amongst the acute infective diseases. The vulnerability of the blood in childhood so often referred to renders it peculiarly liable to suffer from the influence of the toxins of such diseases. Though almost all the acute specific fevers show their influence upon the blood in children by a fall in hæmoglobin which sets in just after the temperature has fallen and is only restored during later convalescence,[7] yet the destructive power of some toxins appears to be much greater than that of others. The rheumatic poison seems to be peculiarly potent in this respect. Children rarely fail to exhibit a marked degree of anæmia after an attack of acute rheumatism especially, I think, when accompanied by peri- or endo-carditis. Every fresh outbreak of the disease during convalescence is apt to signalise itself by a deterioration of the blood. This rheumatic form of anæmia which must be familiar to every clinical observer has been specially studied by Dr. A. E. Garrod who has shown that the fall in the red corpuscles in these cases is usually very rapid and may easily amount to 1,000,000 in the course of four or five days. It is interesting, too, to note that sudden and marked falls in the hæmoglobin may occur independently of those in the red cells. The destruction of blood in these cases bears no necessary relation to the height of the fever nor is it influenced by the administration of salicylates. The destruction of red cells is usually speedily made good after the temperature has fallen, but in some cases the diminution of hæmoglobin persists far into convalescence and long after the patient's condition has improved in every other respect. Diphtheria is another of the acute infectious diseases which is apt to be attended by severe blood destruction. It is also characterised by a tendency for myelocytes to appear in the blood—a sign always of bad prognostic omen. The influence of the toxins of the pyogenic organisms is seen in the anæmia associated with oral sepsis in childhood to which Hollopeter[8] has specially drawn attention and in the pronounced anæmia which results from long-standing suppuration. Of mixed causes of secondary anæmia in childhood the syphilitic cachexia, tuberculosis, and chronic diarrhœa may be taken as examples. These probably act both by increasing blood destruction and by interfering with its formation. In these and in all secondary anæmias there is no characteristic type of blood and the extent and degree of destruction are of more value in gauging the intensity of the disease and in forming a prognosis than in making a diagnosis.

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[7] Widowitz: Jahresbericht für Kinderheilkunde, Band xxvii., p. 380, 1888.

[8] Medical News, August 30th, 1902.

INFANTILE SCURVY.

The condition of the blood in cases of infantile scurvy raises questions of great interest and importance. The general pathological anatomy of this disease has been so fully worked out by those distinguished Fellows of this College, Dr. W. B. Cheadle and Sir Thomas Barlow, that there remains nothing of importance to be added from that side. It will be admitted, however, that we are still very much in the dark as to the actual change in the blood which is present in this disease. Now, in the first place it may be remarked that the microscope affords us no help here. An examination of the blood in cases of scurvy shows that it exhibits merely a varying degree of that secondary anæmia of rather chlorotic type which is so frequent in rickets and other conditions of impaired nutrition. Nor does histological examination of the marrow which I have been able to carry out in two cases reveal any characteristic changes. We are driven, then, to study the question from the chemical point of view. It will be obvious that this is an investigation attended by great difficulties. One cannot obtain a sufficient quantity of blood to subject it to accurate chemical analysis and accordingly one is compelled to study the subject indirectly. In the course of the last few years I have tried, at the suggestion of Dr. Garrod and as opportunity offered, to arrive, by a process of therapeutic experiment, at an idea of what the chemical fault in the blood of these cases is. My progress towards a solution of the problem has been slow, for cases of infantile scurvy are not numerous and not all of them are suitable subjects for such observations as I am about to describe, but it may be worth while to put before you the results so far as I have gone in the hope that they may lead to more extended observations on the same lines by others.

It will be generally conceded in the first place that infantile scurvy is the result of a faulty diet. The first question that arises then is this: Is the fault a positive or a negative one? That is to say, is there present in the food some constituent which it should *not* contain, or is there absent from it or present in insufficient amount one of its normal ingredients? To this question the general study of the etiology of the disease has not afforded any satisfactory reply. It has shown only that the vast majority of cases develop when the child is being fed upon a diet which is deficient in fresh constituents, particularly in fresh milk. As to how it is that such a diet produces the disease no explanation is forthcoming. It has been referred by some to the presence of poisonous constituents (ptomaines) in tinned foods, a view which as regards adult scurvy, at all events, is believed to have received support from the experiments of Vaughan Harley on monkeys. Others have referred the injurious effect of sterilised food to the absence in them of some mysterious ferment. The first step, then, must be to see whether, leaving the diet under which the disease developed alone, one can, by the mere addition of certain constituents to it, effect a removal of the symptoms. Fruit juice is the material which one naturally thinks of adding and in order to elimininate the ferment theory I have given it in a sterilised form. In Case 2 of Table II. this was added to the diet, no other change being made, and the result showed that it had a distinctly curative influence.

The inference to be drawn from this observation and from that on Case 1 is that the fault in the diet of scurvy is one of omission and not of commission, in that fruit juice contains something which the blood in this disease lacks and that this ingredient is of an "unorganised" nature. The next step was to administer the constituents of fruit juice separately and so to arrive by a process of exclusion at the particular ingredient concerned. By means of dialysis the crystallisable were separated from the uncrystallisable constituents of the juice and the dialysate was evaporated down until it was equal in bulk to the original quantity of juice. Preliminary observations on cases not included in the accompanying table showed that the uncrystallisable or colloid constituents were devoid of any curative effect. The dialysate was then tried (Cases 3 and 4) and proved to have a distinct power of ameliorating the disease. The assumption seemed justified therefore that the curative agent is contained amongst the crystalline constituents. The final proof of this would be found if one could show that the administration of an artificial mixture of the vegetable salts found in fruit juice is also followed by cure. Here, however, the results are not so satisfactory. I have tried the effects of administering potassium tartrate potassium citrate, and potassium malate (the chief saline constituents of fruit juice) in considerable doses but have not been able to obtain anything like such good results as with the natural juice (see Cases 5, 6, 7, and 8). That these salts, however, have, even in their artificial form, a power of restraining the disease I think there can be no doubt, and my friend Dr. John Thomson tells me that he has seen a case in which scurvy was kept in check so long as citrate of potassium was being administered for other reasons.[9] It may be that these salts are less active in their artificial form than in that in which they occur in the natural juice, just as it is well known that a natural mineral water is often more active than any artificial imitation of it. At all events, I think the conclusion is provisionally justified that the defect in the blood which causes the symptoms of scurvy is a poverty in vegetable salts, a conclusion which I need not point out is in no way a novel one, though it has never, so far as I know, been put to any systematic test.

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[9] Dr. Thomson writes that the case alluded to was that called "Baby B." in his paper on Acute Pyelitis in Infants (Scottish Medical and Surgical Journal, July, 1902). She had been brought up mainly on sterilised milk and cream mixture, but to this two meals of gruel and one of Nestlé's food had been added for a short time. She had apparently thriven well enough till nine and a half months old when she got mucous diarrhœa and some pain on movement of the left leg. When first seen a fortnight later her symptoms were those of acute pyelitis but her gums were also red and swollen. There were no other scorbutic manifestations. Sterilised milk was continued and citrate of potash was administered for the pyelitis which soon disappeared. A few days after it was stopped, however, distinct scorbutic symptoms appeared—viz., marked sponginess of the gums and large bruises on both shins. Under the usual dietetic treatment she recovered rapidly.

A priori reasoning would lead to the conclusion that the citrates are the vegetable salts chiefly concerned. It must never be forgotten that fresh milk is surprisingly rich in citric acid. It has been calculated, indeed, that three pints of it contain from 50 to 60 grains of citrate, or about as much as is contained in an ounce of lime juice. In milk the citric acid is combined with calcium as citrate of lime. Corlette, in an interesting paper read before the British Medical Association in 1900, has shown that the calcium citrate of milk occurs in the amorphous and more soluble form, its solution being aided by the presence of phosphates. When milk is boiled the amorphous is converted into the crystallisable form of the salt which is less soluble and separates out. The mere boiling, and *a fortiori* the sterilisation, of milk therefore causes it to become poorer in citrates than it ought to be, and to this he attributes the development of scurvy when such milk is exclusively used. Ingenious and simple though this explanation is, it cannot yet be regarded as proved. I have certainly found that the artificial administration of calcium citrate is of even less therapeutic power in scurvy than are the artificial salts of potash (Case 5). In any case it must be admitted that the hypothesis of a deficiency of vegetable salts in the blood does not bring us much nearer an understanding of how it is that the hæmorrhages and other characteristic symptoms of the disease are brought about. Certainly it is not in a reduced coagulability of the blood that the explanation is to be found. Whatever may be the case regarding the coagulability of the blood in scurvy of adults it is apparently not in any way lessened in the infantile form of the disease. I have tested this point in five well-marked cases, using Wright's coagulometer, with the following results :—

Age.	Coagulation time.
Eight months	3¾ minutes.
Eleven „	4½ „
?	4¼ „
One year	5¼ „
One „	4 „

This gives an average coagulation time of about four and one-third minutes which closely corresponds with the normal. One effect, however, which one would certainly expect to ensue upon a diminution of vegetable salts of potash in the blood is a reduction in its alkalinity. Whether such diminished alkalinity is actually present in infantile scurvy I have not myself been able to test, but Dr. A. E Wright informs me that he has investigated the point in several cases with the aid of his ingenious apparatus for testing the reaction of the blood and has found that a diminished alkalinity actually exists. Such an occurrence would not be at all at variance with the results of general clinical observation on the etiology of the disease. Everyone must have seen cases of scurvy in which the mere stoppage of the use of a tinned food without anything being substituted for it or other change made in the diet has been followed by the happiest results. Now the cereal foods, as Wright has shown,[10] certainly yield a more acid ash than milk and what happens probably in such cases is that there is a disturbance of the proper balance of acid and alkaline constituents in the blood, a balance which is readjusted when the supply of the more acid salts is withdrawn. Wright has established this in the case of adult scurvy by an examination of the blood of soldiers who suffered in the siege of Ladysmith[11] and has, as already stated, found a similar condition of the blood in cases of infantile scurvy. It seems likely, therefore, that it is upon such lines as those indicated above that the explanation of the ultimate cause of the disease must be sought.

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[10] Army Medical Reports, 1895.

[11] THE LANCET, August 25th, 1900, p. 565

LECTURE II.[1]

ANÆMIAS ASSOCIATED WITH ENLARGEMENT OF THE SPLEEN.

MR PRESIDENT AND GENTLEMEN,—In no section of our knowledge of the blood disorders of early life does greater confusion exist than in regard to that group of anæmias which have as their most striking clinical feature a more or less pronounced enlargement of the spleen and in none are the views of different writers more conflicting. Yet this group includes some of the most striking examples of anæmia met with clinically in childhood, cases, moreover, which are peculiar to this time of life. It is therefore of the first importance that we should try to arrive at some clear ideas as to their nature and relationships. As a preliminary to further study it will be necessary to review briefly the present state of our knowledge as to the functions of the spleen in health.

FUNCTIONS OF THE SPLEEN.

The progress of our knowledge of the diseases of the spleen has long been retarded by the insufficiency of our information as to the rôle which it plays in the physiology of the body. Ever since the time of the Italian anatomists it has been known, indeed, that the spleen is not essential to life. Whatever it does we can get on without it, for its functions seem to be easily capable of being taken up vicariously by other organs. Of these functions that which seems most clearly established is the part which the organ plays as a filter in removing from the blood stream any foreign particles which it may contain. This has been proved experimentally in the case of particulate substances artificially introduced into the blood and almost certainly occurs physiologically in the removal of the débris of red and white cells which have been broken down in the circulation. Enlargement of the spleen in disease may occur as a response to an increased demand for the performance of these scavenger functions and this, no doubt, explains the splenic enlargement met with in acute infective diseases and in malaria. But such enlargement is usually neither great nor persistent and chronic massive enlargement of the spleen in anæmia is certainly not thus to be explained.

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[1] Delivered on March 10th.

Like all organs which contain adenoid tissue the spleen can claim to be a seat of formation of lymphocytes. This is a function which is probably of considerable activity in the child in whom the Malpighian bodies are normally both large and numerous. This lymphogenic function, however, is one which the spleen shares with many other organs and notably, in the child at least, with the thymus, and even when the spleen is completely removed no reduction of the number of lymphocytes in the blood occurs. Their number on the contrary is then increased, apparently from an over-compensation for the loss of the spleen by the lymphatic glands. Ehrlich, indeed, goes so far as to say that an increase of the lymphocytes, so long as an affection of the lymph glands can be excluded, should be referred to functional exclusion of the spleen. This is a point of great importance, for, as we shall see, one of the features of many cases of anæmia with splenic enlargement in childhood is just such a lymphocytosis. In addition to lymphocytes some writers have referred to the spleen a share, at least, in the production of the large mononuclear cells, but this cannot be regarded as finally proven.

There is some reason to suppose that during part of intra-uterine life the spleen helps in the formation of red corpuscles, but there is no evidence that this persists as a normal function after birth.[2] On the other hand, Dominici and others believe that, if over-active, the spleen can assume myelogenic functions and give rise both to red cells and to myelocytes. This happens after experimental bleeding and Wolff[3] cites cases in which he has found evidence of the existence of such a function. He is of opinion that the spleen contains "indifferent cells" which can develop along various lines according to the demand of the moment. Normally they produce non granular white blood corpuscles, but if the function of the marrow is interfered with they can produce both red cells and granular leucocytes. If such an occurrence is indeed possible then it is in the child particularly that one would expect to meet with it, for in early infancy there is reason to believe, as we have already seen, that specialisation of function on the part of the blood-forming organs has not been carried so far as in the adult.

We may now turn to the proper subject matter of this lecture—the anæmias associated with splenic enlargement, and begin by a study of that group of cases which may be classed for convenience as

SPLENIC ANÆMIA OF INFANCY.

Everyone who sees much of disease in children must be quite familiar with the clinical characters of the cases which I propose to group together under this heading. The patient is usually somewhere between six months and two years old. Generally there is some wasting and sometimes this is extreme. The complexion is waxy or sallow, often with a slightly yellow tint resembling that of chlorosis. Rickets is almost invariably present but not usually in an extreme degree. There is a special tendency for the cranial bones to be affected and to show marked bosses in the parietal and frontal regions. The liver is usually somewhat enlarged but not greatly so, and the accessible glands are in many cases readily palpable but never attain any great degree of enlargement. Catarrhal complications such as diarrhœa or bronchitis are often present and death when it occurs is usually due to some intercurrent disease, most commonly broncho-pneumonia. There is no great tendency to hæmorrhage in these cases although epistaxis sometimes occurs. In severe cases a petechial eruption may make its appearance and is usually of ill omen, for few cases which exhibit it recover. Special interest attaches to the relationship of these cases to congenital syphilis and to rickets. Of 42 well-marked cases of which I have notes congenital syphilis was undoubtedly present in six, in 15 it was doubtful, and in 21 (or 50 per cent.) it could be excluded, so far at least as that is ever possible. Rickets was markedly present in 26 and of these 20 exhibited cranial bossing in a greater or less degree. In 13 there was only slight rickets and in three it was entirely absent. The significance of these figures we shall return to later.

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[2] See Paton and Goodall, Journal of Physiology, vol. xxix., p. 411, 1903.

[3] Zeitschrift für Klinische Medicin, Band xlv., p. 385, 1902.

Some facts in the family history are of interest. There seems to be a tendency for the disease to occur in more than one member of a family. Twins seem specially liable to suffer. I have seen this four times and the same fact has been pointed out by Fowler and others. In the last lecture, it may be remembered, the tendency for some other forms of anæmia to affect twins was mentioned and possible reasons for it were discussed. I have a general impression, also, although it is difficult to bring it to the test of statistics, that the disease is commoner amongst children of Jewish parentage than others.[1] I certainly have notes of a large number of such cases and the point is of interest as bearing upon the supposed relationship of the disease to congenital syphilis which it will be generally admitted, I think, is rather uncommon amongst the Jews. The existence of tuberculosis in the family is a common fact in the clinical history of these patients but it is difficult to be sure if it is found with a frequency which can be described as greater than that met with in the ordinary run of hospital patients. Certainly the patients themselves do not appear to be more subject to tubercle than other children.

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[1] This has also been pointed out by Clive Riviere.

TABLE III.—CASES OF SPLENIC ANÆMIA OF INFANCY.*

No.	Sex and age.	General clinical characters.	Rickets.	Congenital syphilis.	Spleen.	Glands.	Red corpuscles.	Hæmoglobin per cent.	Total white cells per cubic millimetre.	Absolute number of uninuclears per cubic millimetre.†	Absolute number of polynuclears per cubic millimetre.†	Differential count (percentages). Polynuclears.	Large mononuclears and transitionals.	Lymphocytes.	Eosinophiles.	Myelocytes.	Result.
1	F., 24 months.	Ill for a few weeks; marked pallor; hæmic murmurs.	Very slight.	(?)	To umbilicus.	Slightly +	1,800,000. Many microcytes and oval forms. No nucleated red cells.	26	1,800	885 (−5715)	887 (−4273)	49·3	7·6	41·6	1·5	—	Died from noma ten months after first coming under observation.
2	M., 12 months.	A twin; always delicate; chlorotic complexion; hæmic murmurs.	Marked head bosses.	—	„ „	Definitely +	3,200,000. Unequal in size; some poikilocytosis, a few nucleated.	25	10,920	7469 (−651)	3276 (−2324)	30	68·4		1·5	Very few.	Death from broncho-pneumonia.
3	M., 11 months.	Ailing since bronchitis seven months before; wasted, pale.	Marked.	—	Two fingers' breadth below the umbilicus.	(?)	2,324,000	30	16,000	5280 (−2840)	8960 (+3360)	56	3	30	—	3	Improving when lost sight of.
4	F., 18 months.	Ill since measles three months before; pale but not yellow; hæmic murmurs.	Bossed head.	+	To umbilicus.	—	3,800,000. Some poikilocytosis, a few normoblasts.	32	20,000	14,500 (+7900)	5180 (normal)	25·9	74·3		—	—	Died. No post-mortem examination.
5	F., 13 months.	Very pale; wasted.	+ Head bossed.	(?)	Four fingers' breadth below the costal margin.	Slightly +	2,805,000	33	24,000	10,272 (+2152)	13,800 (+8200)	57·5	10·6	32·2	0·5	6·1	Died from bronchitis three weeks after admission.
6	M., 27 months.	Always delicate; no definite illness; olive complexion.	Moderate.	—	„ „	(?)	3,580,000. A few nucleated red cells.	—	15,000	4050 (−1950)	8400 (+3240)	54	11	16	4	5	(?)
7	M., 17 months.	Never well since birth; repeated hæmorrhages; very pale; some purpuric spots.	+	—	Into pelvis.	Very slightly +	3,312,000	28	36,000	20,520 (+13,920)	13,824 (+8664)	38·4	8·6	48·4	0·1	3·5	Improving when lost sight of.
8	F., 9 months.	Wasting and anæmic, one month; following two attacks of diarrhœa and vomiting.	+ Head bossed.	—	To umbilicus.	—	1,040,000	—	34,000	21,080 (+12,960)	12,240 (+6640)	36	4	58	2	(?)	Improving.
9	M., 32 months.	An eight months child; never strong; extreme waxy pallor; hæmic murmurs.	Slight; no bossing.	+	Easily palpable.	—	1,600,000	—	14,000	10,024 (+5424)	3570 (−1630)	25·5	10·38	61·3	2·7	—	(?)
10	M., 12 months.	Pale and wasting for four months; complexion pale but not yellow; hæmic murmurs.	Marked; slight bossing.	—	Half-way to the umbilicus.	—	3,190,000. Not much poikilocytosis; numerous nucleated forms, many of them megaloblasts.	—	35,000	11,900 (+3780)	22,050 (+16,450)	63	14	20·3	0·6	0·6	Died.
11	M., 9 months.	Ailing since birth; pale; badly nourished; general purpuric rash.	Slight; no bossing.	(?)	One finger's breadth below the umbilicus.	Slightly +	3,700,000	—	18,500	12,210 (+4000)	4625 (−1000)	25	8	66	—	(?)	Died six months later.
12	M., 35 months.	Ill off and on since severe diarrhœa six months ago; fairly nourished; earthy complexion; hæmic murmurs.	None; no bosses.	Probable.	Two fingers' breadth below the costal margin.	—	3,000,000	—	25,000	12,500 (+8000)	10,150 (+5000)	40·6	6	49·4	4	—	Improving when lost sight of.‡
13	M., 18 months.	Ailing six months; yellowish complexion; well nourished.	+ Moderate bossing.	—	One finger's breadth below the umbilicus.	Slightly +	2,760,000. No nucleated red cells.	—	9,000	2970 (−3600)	5940 (slightly +)	66	33		1	—	Recovered.
14	F., 12 months.	Ill two months; sallow complexion; hæmic murmurs.	Slight; very slight bossing.	—	„	Slightly +	2,750,000	—	52,000	31,720 (+25,120)	14,560 (+9400)	28	7	54	—	7‡	Died.
15	M., 18 months.	Ailing since three months old; prolonged digestive disturbance; pale but not sallow; poorly nourished; slight hæmic murmurs.	Moderate.	—	Half-way to the umbilicus.	—	3,085,000. One normoblast to every 100 white cells.	—	4,000	1560 (−5000)	2408 (−2700)	60·2	7	32	0·8	—	(?) Recovered.
16	M., 36 months.	Ill for three months; pale but not chlorotic; fairly nourished; liver enlarged and firm; some ascites.	Slight.	(?)	Very greatly enlarged.	—	2,000,000. Some poikilocytosis; a few normoblasts.	40	120,000	95,160 (+88,560)	11,400 (+6240)	9·5	79·3		6	4·2	(?)
17	M., 10 months.	Wasting since six months old; long-standing constipation.	Slight.	(?)	One finger's breadth below the umbilicus.	Palpable in the neck.	3,835,000. Marked poikilocytosis; 14 normoblasts to 100 white cells, many showing mitosis.	23	15,000	10,500 (+2380)	3780 (−1820)	25·2	18·8	51·2	1·6	3·2	Died from whooping-cough.
18	F., 24 months.	Ill for six months; chlorotic complexion; liver slightly enlarged.	Distinct.	+	—	Slightly enlarged all over.	4,072,000. Moderate poikilocytosis; normoblasts numerous.	32	52,000	31,200 (+24,600)	11,960 (+6800)	23·3	41·3§	18·7	2·8	13·8	Died.
19	M., 11 months.	A twin; pale since birth; bottle-fed; has had frequent diarrhœa.	Distinct; slight bossing.	—	Four fingers' breadth below the ribs.	Slightly enlarged in the neck.	1,940,000. Marked poikilocytosis and many normoblasts.	34	16,100	8320 (normal)	7280 (+1680)	45·5	52		2·0	0·5	(?)
20	M., 11 months.	Co-twin of the above; same history and symptoms.	„	—	Three fingers' breadth below the ribs.	„	3,260,000. Poikilocytosis and many normoblasts.	36	18,700	11,220 (+3100)	7106 (+1506)	38	60		—	2	(?)
21	M., 12 months.	A seven months child; pale since birth; bottle-fed; suffers from head-nodding.	Slight.	+	Four fingers' breadth below the ribs.	—	1,765,000. Poikilocytosis well marked; two normoblasts to 100 white cells.	26	4,500	2430 (−5690)	1935 (−3665)	43	54		3	—	Died
22	M., 13 months.	A seven months child; yellowish complexion; general œdema.	Slight; head bossed.	Probable.	Enormously enlarged.	(?)	2,585,000. Considerable variation in size; some poikilocytosis; 13 per cent. of normoblasts, many showing mitosis.	23	9,350	5002 (−3118)	3459 (−2141)	37	12·5	41	—	9·5	(?)

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* Since this table was constructed a very similar one has been published by Dr. J. H. Drysdale and Dr. Hugh Thursfield in a paper read before the Royal Medical and Chirurgical Society on Feb. 9th, 1904. As both tables are based largely on the records of the Hospital for Sick Children, Great Ormond street, many of the cases included in them are identical. † The figures within brackets indicate the absolute excess or deficit of each kind of cell per cubic millimetre, calculated on the basis of the normal numbers at different ages, as described in the first lecture. ‡ A considerable number with basophile granulation. § Most of these were large round cells with diffusely staining nucleus and protoplasm, the latter often with fine basophile granulation, some with mixed granulation.

Blood changes.—The characters of the blood are of special interest (*vide* Table III.). The red corpuscles are always reduced in number but rarely to an extreme degree. From two to three millions per cubic millimetre is the common figure and I have never seen a case in which they fell below one million. Fowler records a case in which they were normal in number, but I have never met with such myself. The hæmoglobin is always reduced but not necessarily in proportion to the reduction of red cells, and bearing in mind the low ratio of hæmoglobin which is normal to infancy the percentage may be only slightly reduced. As in all severe anæmias in childhood the red corpuscles are apt to vary a good deal in size, large forms being often met with. More or less of poikilocytosis is usually present, but it is seldom of extreme degree.

Much importance has been attached to the presence of nucleated corpuscles in the blood in this disease. They are certainly usually present but it must be remembered that, as already pointed out, nucleated cells are apt to appear in all severe cases of anæmia in young children and I am not sure that they form a more striking feature in the blood of this disease than in grave secondary anæmias. The majority of them are normoblasts, the nuclei of which often exhibit signs of division, but megaloblasts are also met with. Fowler found them in 13 out of 20 cases and they certainly do not have the same grave significance as attaches to their presence in the blood of the adult. It is difficult to know indeed what impertance can be attached to the occurrence of nucleated red corpuscles in the anæmias of childhood. In the cases under consideration at all events they exhibit no constant relation either to the total number of red cells or to the degree of leucocytosis. A reference to the table will show that nucleated red cells may be abundant even although the red corpuscles themselves are not greatly reduced, and a high degree of leucocytosis is not necessarily accompanied by the presence of a high proportion of normoblasts. A leucocytosis is usually present in these cases but not invariably. A reference to the table will show that in a considerable number of cases the total number of white cells is actually reduced. An increase, however, is commoner, but the tendency is to over-estimate it, forgetting that between the ages of one year and 18 months, at which the majority of these cases is met with, the number of leucocytes is normally from 12,000 to 14,000 per cubic millimetre. In order to avoid confusion on this point I have calculated the absolute numbers of granular and non-granular cells per cubic millimetre in each case (see table). It will be observed that in a few cases an absolute increase in the granular cells occurs. In some instances this is undoubtedly due to an ordinary leucocytosis called out by the existence of complications, such as broncho-pneumonia, but in others no such cause could be discovered. More usually the increase is chiefly to be ascribed to an augmented number of non granular cells in the blood. One can see in this an exaggeration of the normal characters of the blood of infancy and another illustration of the tendency for the adenoid tissue to be affected specially at this time of life. The increase in the non-granular cells tends particularly to affect the larger lymphocytes and the large mononuclears, but every intermediate grade between those and the ordinary small lymphocyte is met with, so that exact differential counting becomes difficult. There is, in fact, a marked polymorphism in the leucocytosis in these cases just as there is in cases of myelogenous leukæmia. Myelocytes are usually present, perhaps in all if carefully looked for. The highest proportion I have seen has been 13 8 per cent. (Case 18) ; usually they number 2 per cent. They are often small in size and exhibit but sparse granulation. The eosinophiles never appear to be affected but in a few cases I have found mast cells markedly increased. The bearing of the blood changes on theories as to the nature of the disease will be discussed later ; meantime it may be pointed out that clinically they are chiefly of importance from the point of view of prognosis. In this respect they afford more trustworthy criteria than any other feature of the disease. The degree of splenic enlargement, for instance, appears to be of little import ; on the other hand, the lower the number of red cells and the higher the number of white cells the more severe must the condition be regarded. Further, the more polymorphic the blood—that is to say, the greater the number of large lymphocytes and myelocytes present—the worse is the outlook.

PATHOLOGY.

In proportion to the amount of clinical interest which cases of this group have excited but little attention has been paid to their morbid anatomy and pathology and the descriptions of those who have written upon the subject are mainly confined to the changes met with in the spleen. So long ago as 1886 Stilling[5] described changes in the spleen of rickety children with anæmia, changes which, he said, he had never found in the spleen of an adult. The centres of the Malpighian bodies in these cases showed the presence of areas of epithelial cells of varying size, with protoplasm for the most part homogeneous but containing a few granulations at the periphery and sometimes fat droplets or pigment grains. These cells stained badly and presented a large round or oval nucleus. The mass of lymphocytes surrounding these cells was often so broad as to suggest to this observer an over-activity of the follicle. Sometimes the follicles were very small and not visible at all to the low power but on more careful examination were found to be represented only by small masses of the above cells which

[5] Virchow's Archiv, Band ciii.

had undergone degeneration and vacuolation, the whole appearance giving the impression of a degenerative process. In true cases the follicles are often sharply marked off from the spleen pulp by many concentric layers of densely packed spindle-shaped cells, which form a sort of capsule for the degenerated Malpighian body. Stilling thinks that those appearances indicate an attempt on the part of the spleen to form new cells but that the regenerative elements have undergone degeneration before perhaps they have had time to divide.

Luzet[6] gives a fairly detailed description of the morbid anatomy in one case. He notes in the spleen the existence of perisplenitis but the absence of any increase in thickness of the trabeculæ. The Malpighian bodies were absent but he gives no detailed description of any change in them. He attaches much importance to the absence in the pulp of the large multinuclear cells which he believes to be normally the originators of red corpuscles and concludes from this that the spleen in spite of its size is not taking any active share in the regeneration of the blood. He lays great stress upon the appearance of the liver in his case which presented the fœtal characteristics of indistinct lobulation and showed numerous nucleated red corpuscles between the columns of hepatic cells. Here and there large cells were to be found with nuclei which were often spindle-shaped, exhibited signs of segmentation, and possessed granular protoplasm. These cells he regards as hæmopoietic in nature and on the strength of their presence he considers the essential visceral change in the disease as a resumption of blood-forming functions on the part of the liver. He found the marrow of the femur to be red and rather diffluent. It did not appear to him that the multiplication of red cells in it was very active. Fat was only present in the marrow of the medullary cavity. Mya and Trambusti in a paper published in 1892[7] refer to the changes found by Cardarelli and Fedé[8] and describe the morbid anatomy of two cases of their own. They regard the changes in the spleen as resembling those described by Banti in splenic anæmia—viz., chronic splenitis with hypertrophy of the usual connective tissue of the pulp, much of which had undergone hyaline degeneration. The pulp contained numerous normoblasts with nuclei undergoing mitosis. The Malpighian bodies were atrophic and some of them were converted into mere fibrous knots. The liver in these cases was fatty and they describe the presence in the liver capillaries of multinucleated cells such as those to which Luzet attaches so much importance. They found a great formation of new capillaries in the lymph glands. Fedé,[9] in the joint paper which he wrote with

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[6] Etude sur les Anémies de la Première Enfance, Paris, 1891.

[7] Lo Sperimentale, vol. xlvi., p. 359.

[8] Atti del Primo Congresso Pediatrico Italiano, Napoli, 1891.

[9] Quoted by Wentworth, Boston Medical and Surgical Journal, No. 17, 1900.

Somma, in dealing with the pathology of the disease stated that the glands were normal or slightly enlarged, that the liver was often enlarged from congestion and that there were slight increase of connective tissue and cloudy swelling; fatty degeneration and atrophy of the liver cells might be present in some cases. The spleen, he said, was very large firm, and dark red on section, its connective tissue was increased, the pulp was rich in lymphatic cells, and the follicles were hyperplastic. Glockner[10] in 1898 described the microscopical characters of the spleen in four well marked cases of the splenic anæmia of childhood. He summarises his observations thus. There is a varying degree of thickening of the capsule and also of the septa. There is also a general thickening of the reticular framework, forming a network of enlarged and coarse fibres with definite meshes. Where this process is most advanced the fibres fuse together into more or less homogeneous bundles. There is marked thickening of the adventitia of the smaller arteries in every case and a general anæmia of the whole organ is also striking. The Malpighian bodies, apart from thickening of their reticulum, show no marked changes and are well defined. The specific elements of the pulp also exhibit in only a few places any real hyperplasia, much more generally some degree of atrophy. Only two elements are evidently overgrown—the epithelioid cells of the pulp and, to a less extent, the endothelia of the vessels. The former are probably derived from the fixed cells of the connective tissue and as they increase so does the pulp atrophy.

Fowler[11] reports upon three cases but remarks that the results do not throw much light on the nature of the disease. In one of them the spleen was markedly congested but the Malpighian bodies were distinct and there was a considerable excess of eosinophile cells in the pulp sinuses. In a second case the spleen was anæmic, the Malpighian bodies were distinct, and there was an even more marked eosinophilia. In the third case the pulp was much hypertrophied and the Malpighian bodies were correspondingly obscured, the condition indeed being not unlike that met with in myelæmia. In this case there was no eosinophilia. In none of the three cases could he find in the liver the hæmopoietic cells to which Luzet attaches so much importance. The bone marrow was satisfactorily examined in one case only and appeared to be normal. Hunt[12] describes two cases of "splenic anæmia with internal hæmorrhages in infants." In both the spleen was dense, the Malpighian bodies were replaced by fibrous tissue, and the fibrous tissue of the pulp was increased, but not so much as the trabeculæ. The enlarged spleen of mere rickets exhibits, he thinks, more change in the trabeculæ and less in the pulp than in these cases, whilst the Malpighian bodies are normal or even exaggerated. Ewing[13] in a case of so-called von Jaksch's anæmia in a child 20 months old found the pulp cells of the spleen overgrown and the follicles much reduced in size and number. Throughout the pulp were numerous collections of small cells with compact or mitotic nuclei. Many of these were normoblasts. There was commencing increase of connective tissue and many of the sinuses were obliterated. The liver showed many small intracapillary foci of cells, many of them undergoing mitosis of which the majority were normoblasts, but others were much larger and granular. Occasionally they were fused together into a mass resembling the multinucleated masses of Luzet. The marrow contained no fat; all its cellular constituents were in a state of hyperplasia. Nucleated red cells were very numerous but eosinophiles were not increased.

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[10] Reference in Schmidt's Jahrbuch. Band cclv., 1897, p. 187.

[11] Brit. Med. Jour., Sept. 6th, 1902.

[12] Transactions of the Pathological Society of London, vol. l., p. 209, 1899.

I have made careful examinations of the organs in five cases of this disease (Cases 1, 16, 17, and 21 in Table III. and in one unrecorded case). The histological changes were neither constant nor identical in all of them. In three of them the spleen showed a diffuse overgrowth of the supporting reticulum of the pulp which tended to encroach upon the Malpighian bodies from their periphery so that the outlines of these were lost and in one case at least (Case 16) they were converted into mere knots of fibrous tissue. The overgrowth of the pulp stroma in each of these cases was accompanied by thickening of the capsule and trabeculæ of the organ which sometimes reached a high degree. In two of the cases, on the other hand (Cases 17 and 21), the Malpighian bodies were large and well defined and there was no overgrowth of the pulp stroma. The pulp spaces were often much congested, but in none of my cases could I find any satisfactory evidence of the resumption of blood-forming functions by the spleen nor was there any excess of eosinophile cells present nor any marked overgrowth of the endothelium lining the pulp spaces or venous sinuses.

The marrow was examined both by films and sections in three cases (Cases 16, 17, and 21 in Table III.). In every case it was abundant and fleshy and showed evidences of great cellular activity. Neutrophile and eosinophile myelocytes were present in large numbers as well as "lymphocytic" marrow cells but it was difficult to be sure whether these were more numerous than in normal marrow from a child of the same age. There was abundant evidence of active red cell formation in all cases but few megaloblasts were observed. The liver was examined in four cases. In two of these it was practically normal. In the others it showed merely fatty degeneration, but in one of an extreme degree. I could find no evidence of the presence of Luzet's hæmopoietic cells. In none was there any decided increase of the interlobular connective tissue. The lymphatic glands were examined in three cases. In two of these no change could be discovered. In one (No. 16) the capsule was much thickened and there was a great overgrowth of the supporting tissue of the reticulum at the expense of the gland parenchyma so that the whole section was solid and fibrous-looking. The change was not like that observed in Hodgkin's disease, there being more fibrous tissue formation and less overgrowth of the endothelial cells of the lymph sinuses. It resembled much more the alterations already described as occurring in the spleen pulp in some of these cases.

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[13] Clinical Pathology of the Blood, p. 237.

Speaking generally, the chief change in the spleen in these cases may be spoken of as a chronic splenitis affecting chiefly the pulp but sometimes invading the Malpighian bodies. There would seem to be no definite relation between the extent of the spleen changes and the degree of anæmia but the change seems to have gone on to the greatest degree of fibrosis in the cases of longest standing. The fatty degeneration of the liver is comparable to that which one finds in all advanced anæmias whilst the condition of the marrow is probably merely compensatory. In the one case in which glandular changes were found the condition seemed to be a chronic adenitis comparable to the chronic splenitis already described.

Before proceeding to discuss the relation of the pathological changes to the clinical symptoms in this disease it may be well to indicate briefly the views as to its nature which have been put forward by those who have written on the subject. Gretsel[14] writing so long ago as 1866 was the first to apply the term "splenic anæmia" to cases of this group. He used the term for convenience and without any theory as to their pathology but simply in order to bring the disease into line with leukæmia splenica and lymphatica as these terms were then used. Italian writers early directed their attention to cases of anæmia associated with enlargement of the spleen in infancy. Somma[15] in 1884 described a series of cases and applied to them the term "anemia splenica infantile." He was followed by Di Lorenzo[16] who first introduced the term "infective" (infettiva) in connexion with these cases, a term which was subsequently adopted by Somma and by Fedé, Cardarelli, and some other Italian writers who have described cases of this group. Most of these writers regarded the disease as due to bacterial infection and describe different forms of micro-organisms found in the spleen which they believed to be the specific cause. Meanwhile von Jaksch[17] described cases of anæmia with splenic enlargement in children which he thought were characterised by reduction of red cells and hæmoglobin, high and persistent leucocytosis, enlargement of the spleen and sometimes of the lymphatic glands and to a less degree of the liver. To these cases he applied the term "anæmia pseudo-leukæmica infantum." Von Jaksch's account, probably because it was published in German and at a time when diseases of the blood were beginning to be studied more accurately than ever before, attracted considerable attention and most subsequent writers have followed his terminology. To later communications it would be unnecessary and tedious to make any special reference as they add but little to our clinical knowledge of the disease, and the pathological facts which they contain have already been described, but an excellent summary of them will be found in a series of exhaustive papers by Wentworth in vol. cxlv. of the *Boston Medical and Surgical Journal.* It is to be regretted on every ground that the term "pseudo-leukæmia" was ever applied to these cases by von Jaksch as it has been the means of introducing great confusion into the descriptions of the disease. For almost everyone who has devoted special attention to the subject must agree with the conclusion of Wentworth, a conclusion which has also been arrived at by the majority of recent writers, that the "anæmia splenica infettiva dei bambini" of the Italian writers and the "anæmia infantum pseudo-leukæmia" of von Jaksch are really different ways of describing the same condition. Von Jaksch, in fact, appears to have based his original description simply on a rather severe example of the disease already described by Italian authors. There is thus no real reason for writing as some do of von Jaksch's anæmia as if it were a special morbid entity and the term "splenic anæmia of infancy" is much less objectionable on all grounds than "pseudo-leukæmia infantum" and it is for that reason that I have made use of it in the present description of the disease.

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[14] Berliner Klinische Wochenschrift, No. 20, 1866.

[15] Archivio di Patologia Infantile, 1884, vol. ii., p. 21.

[16] Archivio Italiano di Pediatrica, vol. viii., p. 175, 1890.

[17] Wiener Klinische Wochenschrift, 1838, and Prager Medicinische Wochenschrift, 1890.

NATURE OF THE DISEASE.

Granted, then, that there exists a clinical group of cases presenting the characters I have narrated and which may be conveniently described under the term "splenic anæmia of infancy," we have next to answer the question: Do such cases constitute a definite morbid entity as clearly marked off from other forms of anæmia as, let us say, myelogenous leukæmia? On the reply to be given to this question different writers hold very different views but they may be divided for purposes of discussion into four groups: 1. Those who hold with Wentworth, Fischl, Morse, and others that the splenic anæmia of infancy is not a definite disease but merely a secondary anæmia which owes its peculiar characteristics to the fact of its occurrence in the early years of life. 2. Those who regard it as merely an aleukæmic stage of a true leukæmia. This view has been specially advocated by Luzet and Troje. 3. Those who consider it to stand half-way between leukæmia and pernicious anæmia, a cross, as it were, between these diseases and partaking of the characteristics of both. This is apparently the opinion of Rotch and Ladd, Engel, and Ewing. 4. Those who consider that the disease is one *sui generis*, which is the position taken up by Alt and Weiss in Germany and by Fowler, Melland, and Drysdale and Thursfield amongst English writers. These different positions must now be briefly discussed.

1. Those who regard the disease as a mere secondary anæmia in which the enlarged spleen is, so to speak, merely an accident, base their position on the absence of any apparent connexion between the blood changes and the splenic hypertrophy. Cases with identical lesions in the spleen—namely, chronic hyperplasia—show varying degrees of anæmia. At times, they say, there are marked changes in the blood and at others the changes are very slight and the degree of leucocytosis shows similar variability. These differences cannot be explained by the duration of the condition in many cases and all that one is justified in saying is that in some of the secondary anæmias of infancy there is a chronic hyperplasia of the spleen and in others not. It may be admitted that many of these statements have much force. There is no definite relationship between the degree of splenic enlargement and the character of the blood in these cases, for the spleen may be very large with slight anæmia or the anæmia may be profound and the splenic hyperplasia by no means excessive. This is by no means so certainly the case as regards the leucocytosis however. I think we can say that there is at least a general ratio between the extent to which the spleen is enlarged and the increase in number of the leucocytes and that these usually vary together. It is the polymorphism of the leucocytosis, however, in these cases which is their most important feature and which distinguishes them, I believe, from the secondary anæmias, just as the polymorphism of the white cells in leukæmia distinguishes that disease from a severe leucocytosis. Even in severe secondary anæmias such as we studied in the last lecture such polymorphism does not occur. Great stress has been laid by the advocates of the view that the splenic anæmia of infancy is merely a secondary anæmia on the association between cases so described with rickets and congenital syphilis. That rickets is a very constant concomitant of these cases may be freely admitted, for all clinical statistics go to prove it. On the other hand, it is equally certain that in a few cases rickets has been absent (Case 12 of Table III.). Nor is there any definite relationship between the severity of the rickets and the degree of splenic enlargement or of blood change. Some of the severest cases show but slight evidence of rickets, whilst severe rickets is often enough accompanied by

no appreciable degree of anæmia. Rickets therefore cannot *per se* produce the phenomena characteristic of splenic anæmia and it seems more reasonable to suppose that when the two coexist they are both the result of some common but as yet unknown cause which operates at one time chiefly in the direction of producing anæmia and at others exerts its effects chiefly upon the blood-forming organs.

The evidence in favour of a causal connexion between congenital syphilis and splenic anæmia is even less convincing. The statistics of my own cases showed that the former disease could be excluded in one half the number of the latter and other observers have arrived at very similar results. That congenital syphilis is capable of producing severe secondary anæmia we have already seen and that it can also give rise to splenic enlargement there can be no question, but the latter when due to the syphilitic cachexia is rarely great in degree and is characterised by its occurrence within the first six months of life (Carpenter), a time at which splenic anæmia does not occur. That congenital syphilis, like any other debilitating condition, may predispose a child to become the subject of splenic anæmia one can well imagine, but that there is any more direct relation between them cannot be admitted.

2. The view that the disease under consideration is merely an aleukæmic stage of a true leukæmia—a stage at which the hypertrophy of the spleen is still able to keep in check the excess of white cells produced by the marrow—has been advocated by Troje[14] but has little to commend it. That such aleukæmic stages do sometimes occur in the course of true leukæmias many recorded cases attest, but no one has ever described a case of splenic anæmia in a child which passed later into a genuine leukæmia. Further, it is to be remembered that, as we shall see later, true leukæmia, at least in the myelogenous form, is excessively rare in early childhood, whilst anæmia associated with enlargement of the spleen is by no means uncommon. That being so it is in the last degree improbable that the one is merely a stage of the other. Add to this that the appearances found after death in the two conditions are by no means similar and the proof seems complete that there can be no identity between them. That some of the severest forms of splenic anæmia in infancy do nevertheless suggest, as far at least as their blood picture is concerned, a mild leukæmia cannot be denied, but the appearance is much more that of a mixed myelogenous and lymphatic leukæmia than a pure form of either disease. To this point I shall return, however, when I come to speak of leukæmia in childhood.

3. The view that the so-called splenic anæmia of infancy stands intermediate between pernicious anæmia and

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[14] Berliner Klinische Wochenschrift, No. 12, 1892.

leukæmia has not been put forward by its authors with any great degree of clearness. It is difficult especially to ascertain whether they mean to imply by it that these two diseases are actually to be supposed to be coexisting or whether it is merely that the blood picture suggests a mixture of anæmia of these two types. That a casual inspection of a typical blood film from a severe case of splenic anæmia might at first suggest a combination of pernicious anæmia and leukæmia may be admitted but the red cells in this disease are rarely reduced in number to the degree characteristic of pernicious anæmia, and from the mere presence of numerous normoblasts or even megaloblasts in infancy our study of the secondary anæmias showed us that no conclusions can safely be drawn, whilst the supposed resemblance to leukæmia has already been dealt with. Further, the post-mortem appearances are not those of pernicious anæmia. The presence of iron in the liver which is so characteristic of the latter disease is not found in splenic anæmia and to the mere presence of red marrow in the shafts of the long bones no importance can be attached, for, as we have seen, it is a normal occurrence during the earlier years of life, whilst the microscopical characters of the marrow do not at all correspond with those found in true pernicious anæmia. This view may also be dismissed as in no wise helping to elucidate the nature of the disease.

4. We come finally to the only remaining theory—viz., that splenic anæmia of infancy is a definite morbid entity—a disease *sui generis*. The grounds upon which the holders of this view base their opinion have already been considered incidentally when I dealt with the presumption that the disease is merely a peculiar form of secondary anæmia and consist, it will be remembered, in the peculiar type of blood change and, in particular, on the polymorphous character of the leucocytosis. It must be admitted, however, that there is more reason to class these cases by themselves clinically than pathologically, for the splenic anæmia of infancy has no pathological anatomy peculiar to itself. The histological changes in the spleen, though perhaps greater in degree, are still only the same in kind as are met with in many other cachectic conditions, notably in rickets and in congenital syphilis. The changes in the enlarged spleen in rickets have been specially studied by Sasuschin[19] in 11 cases. To the naked eye he found that the spleen was firm, its capsule rather thickened, the surface pale, and the Malpighian bodies fewer than normal. The microscope showed a fibrous hyperplasia of the supporting tissue and trabeculæ and thickening of the walls of the arteries. The Malpighian bodies were diminished in size and showed an excess of fibrous tissue at their periphery. Towards their centres groups of endothelial cells, often undergoing

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[19] Jahrbuch für Kinderheilkunde, li., 1900, p. 297.

degenerative changes, could be made out. The endothelial lining of the blood-vessels was often swollen. He regards the change as one of chronic inflammation which interferes with the function of the spleen as a blood former. It will be noted that these changes are practically identical with those found in the large spleen of splenic anæmia of infancy. In the spleen of congenital syphilis I have found very similar changes, many of the Malpighian bodies being fibrous and the whole supporting tissue of the pulp increased in amount.

Nor are the changes in other organs any more characteristic. The presence of hæmopoietic cells in the liver which Luzet regarded as pathognomonic of the disease has not been confirmed by other observers and the changes found in the marrow are not sufficiently striking to justify one in regarding them as distinctive. None the less I side with those who would place these cases for clinical purposes in a category by themselves, for diseases cannot be classified entirely on their pathological anatomy, else would chlorosis cease to occupy a chapter by itself in our text-books. That it is difficult to draw any hard and-fast line between these cases and those of secondary anæmia I admit, for at the lower end of the scale the milder cases merge with those of slight anæmia—usually of a more or less chlorotic type—sometimes met with in pure rickets.[20] At the upper end of the scale we find severe cases which stand, as far as their blood picture is concerned, very close to myelogenous leukæmia though never, I believe, really merging into that disease. It is to these severe cases that the descriptions of the so-called von Jaksch's anæmia specially apply but that they can be sharply distinguished from the milder forms cannot be admitted, for, as the table of cases shows, every intermediate degree of severity is met with. It appears to me that it is better to employ the term "splenic anæmia of infancy" to cover all the cases of every degree of severity rather than to use the description "pseudo-leukæmia infantum" introduced by von Jaksch. For the term "pseudo-leukæmia" is one open to objection on many grounds and has I venture to think been the means of introducing great and regrettable confusion into the whole subject. As to the real causal factor in the disease we are still completely in the

[20] It is noteworthy that those factors which I have already spoken of as being actively operative in the production of the chlorotic anæmia of rickets—viz., prolonged nursing and the occurrence of twin pregnancies—are also often found in the history of cases of splenic anæmia of infancy. The frequency of the disease amongst the Polish Jews in the East-end (on which Clive Riviere has also remarked) is probably due to the fact that very prolonged nursing is a habit of that race. It is interesting to observe that this association was pointed out so long ago as 1849 by Battersby. Writing in the *Dublin Quarterly Journal* for May of that year he says that "tumefaction of the spleen in children seems to be the consequence of undue lactation. I have notes of seven cases whose average duration of suckling is 19 months." He adds that these patients are truly chlorotic and invariably exhibit pica.

dark and I confess I am unable to throw any light on the point. Although enlargement of the spleen seems usually, as a clinical fact, to precede the anæmia, it can hardly be regarded as the cause of the latter, for there is no definite ratio, as we have seen, between the size of the spleen and the degree of blood change and in cases which recover the anæmia may pass off long before the spleen has regained its normal size. It would be difficult to understand in any case, as Wentworth has remarked, how a mere fibrous hyperplasia of the spleen could produce by any means an increased destruction of the blood. I am aware that in the so-called splenic anæmia of adults excision of the enlarged organ has often been followed by cure of the disease, but these two disorders, as we shall see immediately, are really entirely distinct and what holds good of one does not necessarily apply to the other. In splenic anæmia of infancy at all events the crucial experiment of operative removal of the spleen is scarcely admissible, for the disease is not one which is inevitably progressive but, on the contrary, is often spontaneously recovered from. On all grounds it seems much more likely that the enlarged spleen and the anæmia are both the result of one common cause, some specific cachexia, possibly toxic in nature. Such a toxin might affect the spleen in the same way as the syphilitic poison does and at the same time induce an increased destruction of red cells or cause an interference with their formation. It has been suggested by Clive Riviere[21] that such a specific toxin as has been postulated may be of gastro intestinal origin and produced by an abnormal growth of micro-organisms, the consequence of gastro intestinal catarrh and injudicious feeding. This ingenious hypothesis, however, can hardly be true of all cases, for in a considerable number, at least, one fails to find any history of diarrhœa, whilst, on the other hand, gastro-intestinal catarrh is of such frequent occurrence in infancy that one must always be very chary of assigning to it a definite share in the production of any given disease. It should be mentioned, however, that a similar theory has been advanced by Rolleston and others to explain the production of the enlarged spleen of adult splenic anæmia and Hamilton has suggested that the supposed toxin in such cases may owe its origin to an abnormal intestinal flora[22]

The leucocytosis in this disease may be the consequence of an interference with the function of the spleen, an expression of its physiological incapacity, and an indication of the vicarious performance of its function by adenoid tissue elsewhere, just as happens after experimental removal of the organ. Adenoid tissue elsewhere, acting, so to speak, in a hurry, might easily turn out cells of an immature type such as we have seen to be commonly the case in this disease. It is probable that the changes in the marrow are also of the nature of a compensatory hypertrophy, for if the differentiation of function of the adenoid tissue and marrow is less complete in early life than in the adult it may perhaps be the case that the undifferentiated cells of the marrow in this disease develop into non-granular instead of into granular leucocytes. That the osseous changes in rickets have over-production of marrow as a secondary result is very likely, for we have already seen how closely bone development and marrow formation are related. The head bosses in particular which are so constant a feature in splenic anæmia involve a considerable increase in thickness and extent of the blood-forming tissue and may really be as much a hypertrophy of marrow as a bone change.

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[21] Transactions of the Royal Medical and Chirurgical Society, vol. lxxxvii., 1903.

[22] See discussion on Splenic Anæmia, Brit. Med. Jour., Sept. 12th, 1903.

RELATION OF THE SPLENIC ANÆMIA OF INFANCY TO THE SO-CALLED SPLENIC ANÆMIA OF ADULTS.

I have recommended the use of the term splenic anæmia of infancy to cover all the cases in the group we have just been considering and the only disadvantage of adopting such a nomenclature is that it is apt to lead to confusion with the so-called splenic anæmia of adults. This would be unfortunate, for the two conditions are really entirely distinct. It would be going beyond the legitimate scope of these lectures to discuss whether the splenic anæmia of adults is a true pathological entity but most people will agree that the term is at least one of clinical usefulness as covering a group of cases which present a clinical "symptom-complex" in common. Many, indeed, would go further than this nowadays and, regarding splenic anæmia as merely the initial stage of what has been described as Banti's disease, would associate with it a constant course and a definite morbid anatomy. The splenic changes in Banti's disease indeed present many points of resemblance to those found in the group of cases peculiar to children which we have been considering. These changes have been summed up as follows :[23] 1. Atrophy of the Malpighian bodies, brought about either by an overgrowth of the connective tissue ensheathing the central artery or by an encroachment of fibrous tissue from the periphery. 2. Thickening of the capsule and the trabeculæ, the walls of the vessels and of the fine fibrous reticulum forming the walls of the spaces of the splenic pulp. 3. In a minority of the cases there is also a proliferation of the endothelium lining the splenic vessels and blood spaces of the pulp, the proliferated endothelium appearing in the form of large cells with clear protoplasm and a peripherally situated nucleus, the cells in some instances completely filling the blood space.

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[23] Trevor: Ibid., Sept. 12th, 1903.

Here, again, then one finds an overgrowth of supporting tissue in the Malpighian bodies and throughout the pulp generally with an increase of fibrous tissue and a proportionate diminution of the adenoid constituents. It must be borne in mind, however, that but little diagnostic importance can be attached to fibrosis involving the trabeculæ and splenic pulp and to atrophy of the Malpighian bodies. As Rolleston[24] has pointed out, varying degrees of splenic fibrosis are met with in long-continued bacterial poisoning and fibrotic atrophy of the Malpighian bodies has been produced experimentally by Pilliet with metatoluylendiamin, paraphenylene, and sodium nitrate. With the morbid histology of the spleen, moreover, the apparent resemblance between Banti's disease or splenic anæmia ordinarily so-called and the splenic anæmia of infancy ceases. The blood picture in the two is totally different. In splenic anæmia of adults we have to deal with a slight diminution of red cells, a marked diminution of hæmoglobin, and a diminished number of leucocytes—a combination described by Senator as oligocythæmia, oligochromæmia, and leucopenia, which contrasts markedly with the great diminution of red cells, the presence of normoblasts, and the heteromorphous leucocytosis characteristic of the infantile disease. In addition to this the clinical course of the disorder is totally different. Splenic anæmia in adults is a very chronic condition which extends over years but is slowly progressive and, so far as we know, invariably leads to death. The splenic anæmia of infancy, on the other hand, is of much shorter duration and by no means progressively fatal but, on the contrary, is recovered from in a considerable proportion of the cases. If, then, these two conditions resemble each other only in the common factor of presenting some degree of anæmia along with enlargement of the spleen the next question which arises is: Does one ever meet in childhood with cases of splenic anæmia of the adult type? Occasionally, I think, one does. Hamill,[25] for instance, has reported the case of a boy, aged six years, who suffered from anæmia associated with great enlargement of the spleen and repeated hæmorrhages. The blood exhibited anæmia of the chlorotic type with leucopenia, but the relative proportion of the granular and non-granular cells varied at different examinations. He died four years later, death being preceded by the appearance of ascites. The necropsy showed fibrous hyperplasia of the spleen and an increase of connective tissue around the bile ducts in the liver. Hamill does not attempt to classify this case but I think there can be no doubt that it must rank with the splenic anæmias of adult type.

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[24] Discussion on Splenic Anæmia, Ibid., Sept. 12th, 1903.

[25] Archives of Pediatrics, September, 1902.

Another case has been recorded by R. T. Williamson [26] The patient was a boy, aged nine years, whose illness was of two years' duration. There was no evidence of syphilis or rickets. He presented great enlargement of the spleen but not of the lymph glands, with marked anæmia (3,030,000 red cells), and there was no leucocytosis (4000 per cubic millimetre, the lymphocytes being in slight relative excess). There was intermittent pyrexia. He died and the post-mortem examination showed that the Malpighian bodies in the spleen were fibrous. whilst the pulp contained many large cells inclosing red corpuscles. The marrow of the femur was dark red and "lymphoid" and there were some vegetations on the mitral valve and a few ulcers in the small intestine. This case also closely resembles the splenic anæmia of adults but it is difficult altogether to exclude ulcerative endocarditis which seems sometimes to be accompanied by great enlargement of the spleen without any leucocytosis.

In a very typical example of splenic anæmia terminating in Banti's disease described by Rolleston[27] and confirmed by a post-mortem examination the interesting statement is made that the patient, who was 20 years of age, had been an in-patient at the Hospital for Sick Children, Great Ormond-street, for a similar condition 11 years before. Cases of splenic anæmia of adult type do therefore seem to occur in childhood, but owing to the great rarity of that disease even in adult life it is difficult to say with what degree of relative frequency. As far as I can discover, however, such cases are not met with in infancy but only after the period of second dentition—that is to say, when the blood has assumed the adult characters. It is true that Hunt[28] has described two cases of splenic enlargement with anæmia in infants aged eight and 16 months respectively which he believes to have been examples of the adult form of the disease but the blood examination is not given in sufficient detail to enable one to form an exact judgment. So far as it goes one of them certainly seems to have been an ordinary splenic anæmia of infancy. It is true also that one meets with great enlargement of the spleen in infancy associated with more or less anæmia but no leucocytosis which present at first sight a resemblance to the splenic anæmia of adults. Examples of these have been given in Table III. There can be little doubt, however, that those are cases of the ordinary splenic anæmia of infancy on the way to recovery, for on following them out one can often find that the spleen gradually recedes behind the ribs until complete recovery is established. Others are probably merely examples of rickets associated with an unusual degree of splenic enlargement. In later childhood again one sometimes meets with puzzling cases in which there is enlargement of the spleen with more or less anæmia but which one hesitates to class as examples of ordinary splenic anæmia of adults. Some of these may possibly be examples of the primary splenomegaly—endothelial hyperplasia of the spleen—so well described by Bovaird,[29] but others are almost certainly of syphilitic origin. To the latter class the following cases probably belong.

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[26] Medical Chronicle, vol. xviii., p. 103, 1893.

[27] Clinical Journal, 1902, vol. xix., p. 401.

[28] Transactions of the Pathological Society of London, vol. l., p. 209, 1899.

Case 1.—A boy, aged two and a half years, was said to have a lump in the abdomen since he was six months old. There was a definite history of inherited syphilis He was only slightly anæmic, the red cells numbered 4,500,000, the hæmoglobin amounted to 55 per cent., and the white cells to 13,000 per cubic millimetre. There was a slight relative excess of lymphocytes. The spleen reached below the umbilicus and there were well-marked signs of rickets and a slightly bossed head. Under vigorous antisyphilitic treatment the spleen rapidly diminished and ten months later had entirely disappeared.

Case 2.—A boy, aged 11 years, had had an enormously enlarged spleen without other symptoms for upwards of two years. The family history was indefinite but a brother had suffered from "bad eyes." There was no enlargement of the glands or of the liver. The red cells were 4,360,000, hæmoglobin 56 per cent., and white cells 4700; the polynuclear and uninuclear forms were about equal. His subsequent history could not be ascertained.

Case 3.—A girl, aged 11 years, presented well-marked signs of congenital syphilis (notching of the teeth, interstitial keratitis, &c.). The spleen was enormously enlarged; the liver was large and irregular. The glands were not affected. The red cells and hæmoglobin were normal. The white cells numbered 8000 and a differential count showed 65 per cent. polynuclears, 31·7 uninuclears, and 3 per cent eosinophiles. She subsequently died rather suddenly when at home.

In the cases cited anæmia was not pronounced but in a series published by Chiari[30] in young adults anæmia was a marked feature and splenic anæmia was closely simulated. In all these cases the symptoms appeared to have come on about puberty.

Leukæmia in Childhood.

It cannot be said that recent work on leukæmia in the adult has tended to give a sharper definition to our knowledge of the diseases classed under that term or to clarify our notions of their pathology. On the contrary, the division of the leukæmias into two well-defined types which until recently was believed to hold good has been shown to be no longer tenable. The old division into splenic and lymphatic forms, based mainly on clinical differences, had to give way to the pathological classification of lymphatic and myelogenous leukæmia which rested upon the chief kind of cell found in the blood in each case and its supposed seat of origin. But these terms are tending in their turn to lose their applicability as the accumulation of cases and pathological material goes on. It seems no longer possible to speak of lymphatic leukæmia when in some quite typical clinical examples of that form of the disease the only pathological changes have been found in the bone marrow, whilst, on the other hand, the detection of "myelogenous" changes in the adenoid tissue in what seem at the bedside cases of pure myelogenous leukæmia render it difficult to assert dogmatically that this variety of the disease is always due to changes in the marrow alone. It would seem indeed as if the tendency of recent work were to show that the differentiation of function between the bone marrow and adenoid tissue was not so sharp as from the teaching of Ehrlich most people have been inclined to believe, and that in pathological conditions especially a considerable amount of vicarious action can take place in consequence of which the bone marrow no longer confines itself to the exclusive production of granular cells nor the adenoid tissue to the manufacture of non-granular cells and lymphocytes. If this be true of leukæmia in the adult one would expect *a priori* that it would apply with even greater force to leukæmia in childhood, for in the child, as we have already seen, there is reason to suppose that the normal differentiation of function on the part of the marrow and adenoid tissue respectively is less stereotyped than in the adult. We shall see, I think, that this expectation will prove to be correct. It will be convenient to consider first the two extreme and classical types of leukæmia, the myelogenous (so-called) and the lymphatic, and afterwards to glance at the atypical and intermediate forms of the disease.

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[29] American Journal of the Medical Sciences, October, 1900.

[30] Prager Medicinische Wochenschrift, No. 24, 1902.

MYELOGENOUS LEUKÆMIA.

One is struck, in studying the anæmias of childhood, with the extreme rarity of myelogenous leukæmia. A well-defined and relatively not very uncommon disease in adults, it is of the most infrequent occurrence in the child and in the period of infancy is hardly met with at all. The statements in text-books on this point which sometimes seem to point to a contrary conclusion cannot be accepted, for they are apt to be based upon cases described prior to the introduction of modern methods of blood examination, many of which in all probability were really examples of lymphatic leukæmia whilst others no doubt belonged to the group of cases already dealt with under the title of splenic anæmia of infancy. The only case I have seen myself was one which was recently under the care of Dr. Lewis Smith in the London Hospital and which is to be published by him in detail. It presented an extreme and characteristic example of the disease.

The patient, a girl, aged four years and 11 months, had suffered from enlargement of the abdomen for five and a half months. For the past four months she had wasted. There was no marked pallor, the liver and glands were not palpable, but the spleen was enormous, filling the whole left side of the abdomen. Examination of the blood showed the presence of 2,425,000 red cells, 25 per cent. of hæmoglobin, and 1,590,800 white cells. There were four normoblasts to every 100 white cells. A differential count showed the presence of 56·1 per cent. of neutrophile myelocytes, 3·9 per cent. of basophile myelocytes, 9 per cent. of eosinophile myelocytes, 30 per cent. of polynuclears, and 0·7 per cent. of lymphocytes. A few of the myelocytes showed mixed granulations.

As far as I can discover this is the most marked case of myelogenous leukæmia in a young child yet described. I have collected the following probably genuine cases from the literature. Cassel,[31] writing in 1898, states that the authentic cases up to that time were less than a dozen in all. He apparently includes in this number seven cases collected by Monti and Berggrün, none of which, however, can one regard as being quite certainly examples of the myelogenous form. Cassel adds an undoubted case of his own. The patient was a boy, aged eight years, who exhibited marked anæmia and great enlargement of the spleen but none of the liver or lymph glands. The blood showed 3,550,000 red corpuscles, 40 per cent. of hæmoglobin, and 500,000 white cells. Of these 69 per cent. were true myelocytes and 12 per cent. were eosinophiles. Polynuclears and mast cells were numerous but lymphocytes were very scanty. The patient was still alive when the paper was published. Baginsky [32] has described an undoubted case in a boy, aged nine years, who presented all the usual clinical features. The red corpuscles amounted to 2,133,000 per cubic millimetre and the white to 986,000. Of these 56 7 per cent. were myelocytes, 26·1 per cent. polynuclears, and 4 1 per cent. eosinophiles. The nuclei of the myelocytes stained deeply with tri-acid mixture and there were as a rule only indications of granules in the protoplasm. The case was lost sight of before its termination. Monti and Berggrün describe a case in a boy, one year old, which is probably genuine. He was the subject both of congenital syphilis and of rickets and exhibited enormous enlargement of the spleen with some increase in size of the lymphatic glands. The red cells amounted to 1,846.000 and the white to 66,422. The hæmoglobin varied from 23 to 28 per cent. Of the white cells the great majority were large mononuclear forms with fine neutrophile granules. The eosinophiles were also increased but the polynuclears and lymphocytes were diminished. In spite of the small total number of leucocytes in this case it was probably an example of true myelogenous leukæmia. Charon and Gratia [33] describe the case of a girl, aged eight years, who exhibited marked anæmia with great enlargement of the liver and spleen. A blood count made two days before her death showed 880 000 red cells and 305,000 white cells per cubic millimetre, of which 37·1 per cent. were myelocytes.

These cases—five in all—are the only genuine examples of pure myelogenous leukæmia in childhood which a fairly

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[31] Berliner Klinische Wochenschrift, No. 4, 1898.

[32] Jacobi's Festschrift, p. 19, 1900.

[33] Bulletin de la Société des Sciences Médicales de Bruxelles, 1896, p. 63.

TABLE IV.—CASES OF LYMPHATIC LEUKÆMIA IN CHILDHOOD

No.	Author and reference.	Sex and age.	Total duration.	Clinical characters.	Blood.
1	Thomson and Muir (International Journal of the Medical Sciences, April, 1891).	M., 7 years 11 months.	About 5 months.	Enlargement of the liver, glands, and spleen; general scabies; irregular pyrexia; hæmorrhages.	Red cells, 2,500,000 to 721,250; hæmoglobin 40 per cent ; white cells, 93,000 to 379,000, mainly small lymphocytes; very few polynuclears and eosinophiles; a considerable number of large lymphocytes towards the end.
2	Fowler (Edinburgh Hospital Reports, vol. xiii., 1898).	F., 9 years.	6 weeks.	Extreme anæmia; no enlargement of the spleen or of the glands; hæmorrhage into one retina.	Red cells, 510,000; hæmoglobin 15 per cent.: white cells, 100,000; almost no polynuclears; large and small lymphocytes and large cells with pale, indented nuclei, some with basophile granules.
3	Bradley (New York Medical Journal, vol. lxx., p. 923, 1899).	M., 8 years.	8 ,,	Anæmia: great enlargement of the spleen: slight enlargement of the liver; enlargement of the glands in axillæ and groins; bleeding from the gums.	Red cells, 1,850,000; hæmoglobin, 18 per cent.; white cells, 85,000; polynuclears, 3 per cent.: large lymphocytes, 69 per cent.; small lymphocytes, 28 per cent.
4	Reimann (Wiener Klinische Wochenschrift, No. 39, 1899).	F., 9 years.	6 ,,	The spleen from two to three fingers' breadth below the ribs; slight enlargement of the liver and glands; purpuric hæmorrhages and epistaxis; some swelling of the gums, with bleeding.	Red cells, 1,200,000; hæmoglobin, 20 per cent.; white cells, 350,000; polynuclears predominated at first (mostly eosinophile) but towards the end lymphocytes were in large excess.
5	Pollmann (Münchener Medicinische Wochenschrift, No. 2, 1898).	F., 14 days.	Apparently congenital (mother's blood normal).	Petechial hæmorrhages; the liver and spleen were both much enlarged; right-sided endocarditis; the glands were not enlarged.	Red cells, 2,500,000; white cells, one to eight; almost all uninucleated forms with large nucleus and moderate protoplasm devoid of granules.
6	Guinon and Jolly (Revue Mensuelle des Maladies de l'Enfance, tome xvii., p. 262, 1899)	F., 15 years.	40 days.	Profound anæmia; the liver and spleen were both enlarged (slightly); glands (?).	Red cells, 685,000; hæmoglobin, 20 per cent.: white cells, 28,000; lymphocytes, 93 per cent: polynuclears, from 2 to 3 per cent.; large lymphocytes, from 3 to 6 per cent.: eosinophiles

	heilkunde, Band lii., p. 572, 1900).	years.		gradual increase in size of the liver and spleen till they reached the umbilicus.	different counts 76 to 97 per cent. were uninucleated.
8	McCaw (Report of the Society for the Study of Disease in Children, vol. iii., p. 251, 1903).	F., 1 year 8 months.	5 ,,	No rickets or anæmia; the spleen was enormously enlarged; considerable general glandular enlargement; the liver was one inch below the umbilicus; subcutaneous hæmorrhages.	Red cells, 2,200.000; hæmoglobin, 39 per cent; white cells, 810,000, of which 99·2 per cent. were lymphocytes.
9	Author's case (unpublished).	F., 6 years.	11 ,,	Profound anæmia; gangrenous stomatitis; irregular pyrexia; the spleen was half-way to the umbilicus; the liver was three quarters of an inch below the costal margin; the glands were palpable all over; petechial and retinal hæmorrhages.	Red cells, 1,200,000; hæmoglobin, 10 per cent.; white cells, 170,000, of which 98 per cent. were lymphocytes (mostly small),
10	Author's case (unpublished).	M., 13 years,	7 months.	The spleen was just palpable; the liver was slightly enlarged; the glands were enlarged everywhere; hæmorrhages from mucous membranes.	Red cells, 2.000.000; hæmoglobin, 40 per cent.; white cells, 240,000, 98·7 per cent. being lymphocytes of varying size; polynuclears, 1·2 per cent.; occasional myelocyte and eosinophile cell seen; one normoblast to 105 white cells.
11	Einhorn (Medical Record, July 12th, 1902).	F., 9 years.	Several months,	The spleen was large and firm; the liver was two fingers' breadth below the ribs; the cervical and inguinal glands were enlarged.	Red cells, 3,360,000; white cells, 389,000, of which small lymphocytes were 48·7 per cent.; large lymphocytes, 49 per cent.; mononuclears, 1·3 per cent.; polymorphonuclears, 1 per cent.
12	Carpenter (Brit. Med. Jour., August 29th, 1903).	(?)—3½ years.	4 weeks.	Began with sudden pallor; the spleen was from two to three fingers' breadth and the liver two fingers' breadth below the costal margin; the glands were not enlarged; there were a few bruises on the legs.	Red cells, 1,568.000; hæmoglobin, 15 per cent.; white cells, 130,000, of which 99·18 per cent. were lymphocytes (mainly small),

complete search of the literature has enabled me to discover,[34] and it will be observed that only one of them belongs to the period of infancy. Even assuming that a certain number have been missed the result fully justifies the statement already made that pure myelogenous leukæmia hardly occurs in early life. This fact in the natural history of the disease is certainly a remarkable one, for there is nothing in the bone marrow in childhood which would lead one to expect that it would be less likely to become the seat of a leukæmic process than the corresponding tissue in the adult, whilst the ease with which myelocytes appear in the blood in early life even in comparatively trivial degrees of anæmia would have prepared one for quite the contrary result. Until we have some definite information as to the true cause of leukæmia no explanation of the rarity of the myelogenous form in childhood is likely to be forthcoming, but it suggests at least that, as is perhaps the case with pernicious anæmia, the exciting cause of the disease is not operative at this time of life.

LYMPHATIC LEUKÆMIA.

When we turn to the so-called "lymphatic" form of leukæmia we are met with quite the opposite state of things. The comparative frequency of this form in childhood is just as striking as the rarity of the myelogenous variety. It is only in quite recent times indeed that the frequency of lymphatic leukæmia has been recognised. McCrae[35] in 1900 described a case and gave references to other 13 cases which had been published as occurring in children below the age of ten years up to that time.

Table IV. contains some of the most important cases in children published since McCrae's summary was made, whilst one meets in the literature with casual references to many others which have never been published in detail. The records of authentic cases, moreover, are being added to almost daily.

Clinically these cases conform to the characters of the acute form of the disease and they may be roughly divided into the three types described by Guinon and Jolly:[36] (1) those which exhibit profound anæmia with general glandular enlargement with a hæmorrhagic tendency in the later stages; (2) those in which the hæmorrhagic tendency is exhibited from the outset, petechiæ appearing early so that the case may resemble one of infective purpura; and (3) "pseudo-scorbutic" cases in which lesions in the buccal cavity are the most striking feature. The type of cell which predominates in the blood is the so-called large lymphocyte, many of which are probably really identical with the "lymphoid cells" of Wolff. Pathologically they show the changes which have been so often described as characteristic of the lymphatic form of leukæmia—viz., overgrowth of adenoid tissue generally with the appearance of foci of it in situations in which such tissue is not normally visible and a replacement of the normal bone marrow by lymphoid tissue.

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[34] References to other supposed examples—none of which, however, is sufficiently authenticated—will be found in Clive Riviere's paper in the Transactions of the Royal Medical and Chirurgical Society, vol. lxxxvii., 1903.

[35] Gilbert and Weil in a paper in the Archives de Médecine Expérimentale, tome ii., p. 157, 1899, state that up to that time about 60 cases of acute leukæmia had been recorded, of which five were between the ages of one and ten and 17 between 11 and 20 years of age.

[36] Revue Mensuelle des Maladies de l'Enfance, June, 1899.

No satisfactory explanation of the frequency of the lymphatic form of leukæmia in childhood can be given any more than of the rarity of the myelogenous variety. The fact, however, may be correlated with that of the great extent and activity of the adenoid tissue in childhood, to which reference has already been made and which render it peculiarly liable to become the seat of pathological processes of all sorts of which leukæmia is only one form. One is tempted to find in it also some support for the infective origin of the disease which has so often been advocated when one remembers the peculiar liability of children to infection, particularly such as finds access by the throat. On the other hand, those who see in lymphatic leukæmia a process resembling the production of a malignant growth and who speak of it as a "sarcoma of the blood" might point with equal truth to the frequency of that particular form of malignant growth in the earlier years of life. It may be, too, that, as Parkes Weber has suggested,[37] lymphatic leukæmia is to be looked upon as a less differentiated form of the leukæmic process than the myelogenous form of the disease. In other words, we may really be dealing in it with an overgrowth of the original mother cells which are believed to be the progenitors alike of lymphocytes and of the more highly differentiated type of cell known as myelocytes. Lymphatic leukæmia would then be a return to the fœtal stage in which myelocytes have not yet appeared and such a relapse into intra-uterine methods of blood formation may happen more easily in the child than in the adult.

Compared with the acute variety of the disease chronic lymphatic leukæmia is of comparatively rare occurrence in childhood but not more so probably than in adult life. One is met here with the practical difficulty of assigning a limit of duration within which a case shall be regarded as "acute." Any such limits indeed must of necessity be more or less arbitrary in nature. I have met, however, with one case which can be fairly regarded as falling outside the sphere of the more acute type of the disease. It is included in Table IV. (Case 10). Except as regards their duration these cases present no essential difference from those of the more acute form, but the preponderating type of cell in the blood tends to be rather the ordinary small lymphocyte than the larger form of cell met with in the more acute variety of the disease. These cases are chiefly of interest as forming a supposed link between true leukæmia and Hodgkin's disease but to this point we shall return when we consider that disease in detail.

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[37] Transactions of the Pathological Society of London, vol. liv., p. 286, 1903.

MIXED FORMS OF LEUKÆMIA.

So long as it was believed that the two great seats of production of white cells—the bone marrow and adenoid tissue—were functionally entirely independent and that the former in any circumstances could produce only granular and the latter non-granular cells, so long was it believed that myelogenous and lymphatic leukæmia were two totally distinct conditions which did not coexist and between which no intermediate type was found. But later investigations into the mode of origin of the white cells have rendered it probable that this functional specialism on the part of the adenoid tissue and marrow is not so absolute as had been supposed. It is coming to be believed that both myelocytes and lymphocytes have originally a common parent type of cell and that although it is true that in the marrow the development of these is normally in the direction of producing granular cells (myelocytes) and in the adenoid tissue of producing non-granular cells (lymphocytes), yet upon occasion the parent cells may develop in one direction only in both situations, so that the bone marrow may also produce lymphocytes and the adenoid tissue myelocytes. Coincidently with the rise of this view clinical evidence has been accumulating which points to the actual existence of cases in which the blood presents the picture of a mixed form of leukæmia, both myelocytes and lymphocytes being present in large numbers. Wolff[38] has recently published a criticism of alleged cases of this sort and has come to the conclusion that some of them at least must be regarded as genuine examples of mixed types of leukæmia. Now, as has already been indicated, it is just in childhood when the division of labour between the blood-forming organs is presumably less highly specialised, when myelocytes so readily enter the blood stream, and when lymphocytosis is so common, that one might expect cases of mixed type to occur. Wolff, it is true, declines to admit cases in infancy as affording real evidence of the occurrence of mixed leukæmia because of the confusion and perplexity introduced by cases of the so-called von Jaksch's anæmia already considered. It appears to me, however, to be rather an arbitrary proceeding to rule out such cases. True myelogenous leukæmia is, as we have seen, almost unknown in infancy and it may be that when the disease does occur at this period of life it tends to assume not a pure but a mixed form. Case 16 of my series (Table III.) may perhaps have been of that nature. Morse[39] has reported an interesting case which raises a similar problem. It was that of a boy, one year of age, the exact duration of whose illness was uncertain. He was decidedly rickety and presented enormous enlargement of the spleen with some increase in size also of the liver and lymphatic glands. The blood contained 2,900,000 red cells per cubic millimetre and 48,000 white cells. The differential count showed 23·4 per cent. of small lymphocytes, 8·1 per cent. of large lymphocytes and transitionals, 21·4 per cent. of myelocytes, 46·5 per cent. of polynuclears, and 0·6 per cent. of eosinophiles. There was marked poikilocytosis and many nucleated red corpuscles were present, several of them being megaloblasts. The comparatively low percentage of lymphocytes and the high proportion of myelocytes in this case are certainly unusual even for a severe example of splenic anæmia of infancy, and one is inclined to agree with Morse that the case is rather to be regarded as a mixed form of leukæmia. Fowler[40] has recorded a very similar case in a girl, aged 13 months. There was only slight rickets but the spleen was enormous and the liver and lymph glands were also distinctly enlarged. Purpura and epistaxis were repeatedly observed. Repeated examinations of the blood gave red-cell counts varying from 2,950,000 to 3,950,000 per cubic millimetre, while the leucocytes varied between 23,400 and 58,000. The differential counts varied a good deal, the highest percentage of lymphocytes found being 46. Whilst the myelocytes on one occasion rose to 14 per cent. eosinophiles were not increased. Nucleated red cells were very numerous, nearly all of them being normoblasts. The post-mortem appearances are said to have been those of leukæmia. Fowler regarded the case as one rather of leukæmia than of splenic anæmia from the characters of the blood observed during life. Cabot mentions similar cases.[41] Even were one to admit that these cases are to be regarded as examples of severe splenic anæmia rather than instances of mixed forms of leukæmia the same cannot be said of very similar cases met with at a later period of childhood when splenic anæmia has ceased to occur. Stewart and Campbell[42] have recorded such a case in the person of a boy, aged six years, whose illness lasted only three weeks. He presented marked anæmia, with severe and repeated epistaxis. The spleen was not enlarged but there was some enlargement of the submaxillary glands noted. The blood, which was examined just before death and therefore after repeated hæmorrhages, contained only 750,000 red cells per cubic millimetre with 20 per cent. of hæmoglobin and 40,000 leucocytes per cubic millimetre. Of these 25 per cent. were small lymphocytes, 45 per cent. were polynuclears and the remaining 30 per cent. was made up of myelocytes, 3 per cent. being eosinophilic. The red cells showed considerable inequality in size but none in shape. There were no megaloblasts. A case such as this is obviously very difficult to classify. It is evidently one in which the bone marrow is mainly involved and is so far to be regarded as myelogenous but the high relative number of small lymphocytes would point to some implication of adenoid tissue as well. Another of Fowler's cases[43] is more conclusive. It was that of a girl, five years of age, with enormously enlarged spleen, slightly enlarged liver, and slight hard enlargement of all the superficial lymph glands in whom the illness ran a course of 14 weeks. The red corpuscles were below 3,000,000 and the white corpuscles from 240,000 to 257,000 per cubic millimetre. The differential counts showed: small lymphocytes, 7 to 13 per cent.; large lymphocytes, 32 to 57 per cent.; polynuclears, 16 to 22 per cent.; myelocytes, 12 to 27 per cent.; eosinophile myelocytes, 0·7 to 3·4 per cent.; eosinophiles, 0·6 to 2·6 per cent.; and mast cells, 3 to 3·4 per cent. This seems to be clearly an example of a mixed form of leukæmia and was so regarded by Fowler. Many similar cases could be quoted from the literature[44] but enough has been said to show that the frontiers of leukæmia in childhood are very ill defined. Cases occur intermediate in type between splenic anæmia on the one hand and true leukæmias on the other and also between the two classical forms of leukæmia themselves. Such cases may find an explanation if we regard the myelocytes and the lymphocytes as both arising from a common parent type of cell which we may speak of with Wolff as a "lymphoid" cell, which is probably identical with many of the so-called "large lymphocytes" spoken of in the above differential counts. To this common origin both types of leukæmia could be traced back, myelogenous leukæmia being due to the production from it of myelocytes in excess and lymphatic leukæmia to an excessive production of lymphocytes, whilst in the intermediate forms either the parent cells themselves enter the blood along with myelocytes or both myelocytes and lymphocytes are produced from the common cell in excessive number. The trend of opinion which is supported by such cases as those described is certainly in favour of attaching more importance to the type of cell found in the blood and less to its supposed seat of origin, and if I might venture upon a prophecy it is that in future the leukæmias will be classified on the former basis instead of as hitherto on the latter and that we will speak of myelocytic, lymphocytic, and mixed-cell leukæmias, rather than of myelogenous or lymphatic. At all events, it is only along such lines that order is likely to be introduced into the present confusion which surrounds the classification of those anæmias of children which are attended by a marked increase of white cells in the blood.

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[38] Zeitschrift für Klinische Medicin, Band xlv., p. 385, 1902.

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[39] Boston Medical and Surgical Journal, vol. ii., p. 133, 1894.

[40] International Clinics, vol. ii., 1901, series ii., p. 125.

[41] Clinical Examination of the Blood, fourth edition, p. 454.

[42] Montreal Medical Journal, May, 1902.

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[43] International Clinics, vol. iii., 1903, series xlii.

[44] Examples of mixed leukæmia in the adult have been published by Simon (American Journal of the Medical Sciences, 125, p. 984, 1903) and by Wilkinson (THE LANCET, June 20th, 1903. p. 1739), but in both of these the case began as apparently one of myelogenous leukæmia and ended by assuming the lymphatic type. Other examples are referred to by Fowler (loc. cit.).

LECTURE III.[1]

THE THYMUS.

MR. PRESIDENT AND GENTLEMEN,—I have already remarked upon the prominent rôle played by the adenoid tissue amongst the blood-forming organs of early life and have discussed in general terms the probable reasons for its marked development. It was pointed out also that the mere fact of the extensive development of this tissue in the child and its great functional activity probably rendered it specially liable to become the seat of disease. It is to the study of the morbid processes which affect this tissue, a study which is full of difficulty and in which it must be admitted great confusion exists, that I have now to direct your attention.

Prominent amongst the local collections of adenoid tissue met with in the body and of special interest from the air of mystery which has always enshrouded its functions is the thymus gland. A study of the rise and fall of the functional importance of this gland may therefore be expected to throw some light on the functions of the adenoid tissue in general, for there can be little doubt, I think, that the thymus is not possessed of any functions peculiar to itself and distinct from those of the histologically similar tissues met with throughout the body, whilst, on the other hand, its compact structure and its unique situation render it peculiarly easy of study. In the human fœtus the thymus has attained the infantile type by the end of the third month of intra-uterine life, its development being brought about by a transformation of the epithelial cells derived from the hypoblast, and from this period onwards up to the time of birth it increases rapidly in functional activity, so that by the time when intra-uterine development is complete its weight relative to that of the body as a whole has reached its maximum point. From the moment of birth onwards it undergoes a steady decline which, however, is at first very gradual but after the second year goes on at an accelerated rate, although the gland is still possessed of some degree of functional activity up to the period when the growth of the body is complete. The following table from Friedleben's classical monograph on the thymus indicates in a striking way the growth and decline of the gland :—

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[1] Delivered on March 15th

Period of development.	Weight of thymus (in grans) to every pound of body weight.[2]
Third to fifth month of fœtal life	8·5
Sixth to seventh ,, ,, ...	21·6
Eighth ,, ,, ...	27·3
At birth	33·8
First to ninth month	26·5
Ninth month to second year...	22·7
Second to fourteenth years...	10·6

This decline in the growth of the thymus coincides exactly, as we have seen, with a steady diminution in the number of lymphocytes in the blood and may be taken, I think, as the index of a steady diminution in the functional activity of the adenoid tissue generally. We are here again brought face to face with the intimate relation which exists between the adenoid tissue and the growth and development of the body as a whole or in chemical terms with the rate of general metabolism. It is during the period when metabolism is most active that the thymus maintains its greatest weight, and I may suggest in passing that there may perhaps be found in this fact an explanation of the resumption of activity on the part of the thymus in such a disease as exophthalmic goitre, in which the rate of metabolism is usually increased, as well as of its tendency to persist in cases of gigantism and acromegaly.

I have said that the variations in the size and development of the thymus may probably be safely taken as indicating corresponding variations in the adenoid tissue as a whole. It would not be surprising if in a tissue so important as that which we are considering there were large room for the exercise of vicarious function, so that an over-development of adenoid tissue in other parts of the body can take the place of the thymus and *vice versâ*. In favour of this view are the facts that the thymus may be entirely absent and yet growth be unimpaired (Friedleben) in which case presumably its functions are fulfilled by the adenoid tissue elsewhere. In favour of it also are the great individual variations in the size of the gland—variations which are not fully to be explained by mere differences in the body weight, which have struck all those who have made observations on the weight of the thymus at different ages. It is not improbable too that, as Mettenheimer has pointed out, the degree of development of the thymus at any given age varies in different countries and races which would be quite in harmony with the known variability in the rate of growth and development of the body under different conditions of inheritance and environment. In favour also of the vicarious replacement of the thymus are the results of observations on its experimental removal which show that no serious consequences to growth or development ensue, whilst the number of lymphocytes in the blood after the operation is increased rather than diminished, which is exactly what occurs after excision of the spleen and has been alleged by Ehrlich to be due to a vicarious over-activity of the lymphatic glands.

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[2] The gran = six centigrammes, or 0·9 grain.

The great individual differences in the development of the thymus to which reference has already been made render it very difficult to be sure of pathological variations in its size. It was long ago shown by Friedleben that anything which interferes with adequate nutrition reacts with special force upon the thymus, so that its weight is notably lessened in starvation or after wasting diseases. The marked atrophy of the thymus in cases of infantile marasmus was first pointed out by Seydel. Hansen, Farret, and Mettenheimer went further and were inclined to regard the wasting of the gland as primary and that of the body as a whole as secondary, a view which has recently been insisted upon by Ruhräh and others.[3] Such a relationship, however, is very difficult of proof and against it is the fact that experimental removal of the gland is not followed by symptoms of wasting. In the meantime and until more convincing evidence has been collected it seems wiser to regard the atrophy of the thymus as associated with the diminution of growth and metabolism which accompany marasmus rather than as being the primary cause of the latter condition

In discussing *hypertrophy of the thymus* we are again met with the difficulty of fixing upon a normal standard of development. Ruhräh gives the normal average weight of the gland during infancy as 18 grammes. Thursfield,[4] on the other hand, states that the normal weight is usually greatly exaggerated and that the average is between six and seven grammes. Observations on this point which have been made at the London Hospital for some time, but which are not yet ready for publication, tend to show that the weight of the gland varies very greatly in different children of the same age and that no constant ratio to the body weight can be shown to exist. Most observers are agreed, however, that an excessive development of the thymus is sometimes met with in which it may be increased to ten times the normal or more. The majority of such cases have been found, as is well known, in infants who have died suddenly with symptoms of asphyxia and to such cases the term "status thymicus" has been applied. Other writers who regard the enlargement of the thymus as merely a part of a general increase in the adenoid tissue throughout the body prefer to speak of the condition as the "status lymphaticus" or "lymphatism." The association of sudden death with enlargement of the thymus has long been recognised and many cases of it have been recorded but we are still quite in the dark as to the relationship of the enlargement of the gland to the occurrence of death. It would be going beyond the scope of these lectures to discuss this subject in detail, but as such cases, though not very uncommon, have received but scant attention in this country some of the leading views which have been put forward may be briefly indicated. According to one set of hypotheses the enlarged thymus in these cases acts purely mechanically either by direct pressure on the air passages or by interference with the vagus nerves or by exciting reflexly a spasm of the glottis. All these conjectures were subjected to severe criticism by Friedleben who concluded that none of them was tenable. There seems to be no doubt, however, that in some at least of the published cases there was distinct compression of the air passages and it has been suggested that a sudden throwing back of the head may, by vascular congestion, so increase the degree of pressure exerted by the enlarged gland as to induce asphyxia [5] Such an occurrence would be comparable to the sudden death which may occur from the administration of an anæsthetic to a patient who is the subject of goitre. Nor can it be denied that spasm of the glottis may play a part in some at least of the cases, just as it occasionally produces sudden death in laryngismus stridulus though how the enlarged gland can excite such spasm is more difficult to explain.

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[3] The American Journal of the Medical Sciences, November, 1902.

[4] St. Bartholomew's Hospital Reports, vol. xxxviii., p. 129, 1902.

According to the other leading view which has been put forward the enlarged thymus in these cases is not directly the cause of death but is merely an index of a general "lymphatic" dyscrasia which entails a general feebleness of resistance and renders the subject of it liable to sudden death from any cause. Several instances have occurred, for instance, whilst bathing. The very vagueness of such a theory puts it almost beyond the scope of criticism, but I may say that in at least one typical case I could find no increase of the adenoid tissue elsewhere nor any sign of impairment of health.[6] It certainly would be interesting to have an account of the state of the blood in these cases, particularly as regards the number of lymphocytes, but as enlargement of the thymus is almost impossible of diagnosis during life such observations are not yet forthcoming.[7] Of the other affections of the thymus I do not propose to speak, for they are for the most part identical with those to which all adenoid tissue is liable, whilst its comparative immunity to others, such, for example, as tuberculosis, is no doubt due to its not being in direct lymphatic connexion with any mucous surface.

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[5] Leubuscher: Münchener Medicinische Wochenschrift, No. 23, 1903.

[6] Diffuse overgrowth of adenoid tissue throughout the body has, however, been described by several observers in this condition.

[7] Ewing has found a lymphocytosis in one case.

AFFECTIONS OF THE LYMPHATIC GLANDS.

We now approach the consideration of a group of disorders in regard to which more doubt and confusion exist than in respect of perhaps any of the other affections of which I have hitherto spoken. The confusion to which I have referred is traceable to two causes: (1) to the adoption of a clinical classification based only upon the characteristics which can be observed at the bedside; and (2) to an inadequate study of the morbid histology of the affected organs after death. The adoption of a clinical classification would not be open to so much objection were it not that some of the most important criteria upon which such a classification if it is to be of any real value can alone be based have until recently been unavailable and are still too often omitted in the published reports of such cases. I refer especially to the information afforded by a careful examination of the blood. I need hardly point out that it is only within quite recent years that the importance of such examinations has been realised but for a long time it has been customary to label large groups of the cases about to be described with some name descriptive of their grosser clinical characteristics. Hence, an extensive nomenclature sprang up and was received into the text-books and made the basis of systematic descriptions and it is only now that we are beginning to realise how inadequate it is to our needs that names which were believed to indicate some one definite disease may really cover several different pathological processes and that our whole nomenclature requires to be reconsidered and recast. Now I think one may truly say that few things retard the advance of the scientific knowledge of disease more than the existence of a terminology which has ceased to have any real correspondence with clinical and pathological facts and we need not wonder that progress in the investigation of this branch of our subject has been made with but slow and faltering steps. If we think, for instance, of such terms as "lymphadenoma," "pseudo-leukæmia," "malignant lymphoma," or "lympho sarcoma," how vague and indefinite is the impression they convey! When an author describes a case under one of these designations how can we feel any certainty that the conception present to his mind is the same as that which the term employed arouses in our own? But it is hard to slough off outworn pathological creeds and in attempting to deal with these diseases I shall not have the presumption to suggest any brand-new terminology. I shall content myself with the humbler task of trying to give greater precision to some of the terms already in general use and with describing the clinical features and morbid histology of the pathological processes with which I believe them to correspond. Nor, it must be confessed, is the time yet ripe for a final classification, for any such to be of permanent value must be based, I take it, not upon the clinical features alone nor yet upon pathological histology but upon a knowledge of the particular morbific agency at work, of which both of these are but the expression. We await the progress of research to furnish us with this knowledge, and fortunately there are many signs that we are not likely to wait in vain. Meanwhile, in pursuance of the intention indicated above I turn to consider in the light of clinical and pathological observation that group of diseases which specially affect the lymphatic glandular system in early life. I propose, for the sake of greater clearness in this matter, to attempt no rigidly systematic order of treatment but rather to describe as briefly as may be some extreme clinical types of each disease and subsequently to consider the question of the relation of these to one another and the possible existence of intermediate forms.

1. GENERALISED TUBERCULOUS ADENITIS.

The first case to which I wish to direct your attention was that of a girl, aged 12 years, who was admitted into hospital suffering from anæmia with general enlargement of glands. The illness had begun eight months before with the appearance of a lump above the right collar bone. On admission she looked very anæmic; the glands were greatly enlarged in the neck, axillæ, and groins, being in some cases discrete, in others matted together. Neither the liver nor the spleen was enlarged, but there were some moist sounds over the right lung. There was distinct remittent fever which exhibited periodic exacerbations during which the glands became more enlarged and slightly tender. Examination of the blood showed 5,000,000 red cells per cubic millimetre with a decided reduction of hæmoglobin. The white cells varied in number at different examinations from 15,000 up to 70,000 per cubic millimetre and consisted mainly of the polynuclear variety. The patient went steadily downhill, developed signs of pressure on the bronchi, and died three months after admission.

Post-mortem examination showed that the glands were everywhere much enlarged and in part caseous, those in the mesentery being partly calcified. The tracheal and bronchial glands formed a large mass which had compressed the air tubes. There were some soft white nodules of the size of a bean in the right lung and in the muscular substance of the heart. The spleen was considerably enlarged and contained some white masses resembling infarcts. Sections of the glands showed a typical tuberculous structure and the presence of masses of tubercle bacilli.

A somewhat similar case was that of a boy, five years of age, who had suffered for six months from dyspnœa which seemed to ensue upon an operation for adenoids, prior to which he had enjoyed perfect health. He was markedly anæmic and had slight general œdema with effusion into the pleuræ and some ascites. There was enlargement of the glands in both sides of the neck and in the left axilla but the spleen could not be felt. There were signs of pressure on the right bronchus and some scattered patches of consolidation throughout the right lung. There was also a slight degree of irregular pyrexia. The blood exhibited the ordinary changes of a pronounced secondary anæmia along with a considerable polynuclear leucocytosis. Death took place from exhaustion, the case being regarded as one of lymphosarcoma. At the post-mortem examination, however, it was found that there was extensive caseation of the bronchial and mesenteric glands with patches of tubercle in the lungs and extensive ulceration of the intestine. The spleen was healthy. Tubercle bacilli were found in the glands in large numbers.

Such cases as these seem best described as examples of "multiple acute tuberculous adenitis." They are by no means common, but probably correspond to what used to be spoken of by the older writers as acute scrofula. Examples of such multiple glandular tuberculosis were described long ago by Hilton Fagge[8] and by Pye-Smith,[9] and a good example in a woman, aged 23 years, has been recorded by Francis Delafield.[10] More recent cases which may probably be referred to this group have been described by Hutschmann and Stross[11] and by Ferrarri and Comonotti.[12] The chief features of cases of this type are, I believe, these. They tend to occur especially in young subjects. They run a comparatively short course marked by irregular pyrexia often with periodic exacerbations. They exhibit more or less generalised enlargement of the lymphatic glands but not to any extent of the spleen and a pronounced degree of general anæmia accompanied by more or less polynuclear leucocytosis, the only exception to this rule that I am acquainted with being the case recorded by Ferrarri and Comonotti in regard to which it is stated that leucocytosis was absent. They may be regarded, I think, as examples of multiple infective adenitis, the infective agent being the tubercle bacillus.

HODGKIN'S DISEASE.

Somewhat resembling the above in its clinical features, but totally distinct from them, I believe, is the following case :—

The patient, a girl, aged two years and two months, had suffered for a year from enlargement of glands in the neck. When she first came under observation she was markedly anæmic and hard discrete glands could be felt in the neck and groins but not in the axillæ. The liver was slightly enlarged. The spleen was two fingers' breadth below the costal margin and felt hard and nodular. There were some moist sounds over the lower lobes of both lungs and continuous irregular pyrexia. Examination of the blood showed 1,180,000 red cells and 5000 white cells per cubic millimetre. The red cells were very pale and unequal in size and a few normoblasts were present. A differential count of the white cells showed the presence of 51·5 per cent. of polynuclears, 48 per cent. of uninuclear forms, and 0·5 per cent. of myelocytes. Death ensued from exhaustion without material alteration in the characters of the physical signs or blood, the case being regarded as one of tuberculosis.

The post-mortem examination showed great enlargement of the mesenteric and retroperitoneal glands, which on section were hard, pale, and glistening, with, in some, a few spots of caseation. The mediastinal glands were in a similar condition. The liver exhibited on its surface numerous white fibrous plaques which on section were seen to extend into the substance of the organ in the form of dense fibrous septa. The spleen showed the typical "hardbake" characters. The other organs were healthy.

Microscopical examination of the affected organs exhibited the entire absence of any tuberculous structure or of tubercle bacilli in any of the sections examined, but on the contrary the presence in a typical form of the changes presently to be described as characteristic of what for convenience we may still speak of as Hodgkin's disease.

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[8] Transactions of the Pathological Society, vol. xxv., pp. 22 and 238.

[9] Ibid., vol. xxvi., p. 202.

[10] New York Medical Review, 1887, No. 16, p. 31.

[11] Deutsche Medicinische Wochenschrift, 1893, No. 21.

[12] Wiener Klinische Wochenschrift, 1900, No. 52.

In seeking to elucidate further the nature of such a case as this and to outline the features of the group to which it belongs we find ourselves on ground which has been, and still is, the arena of much controversy—controversy the issues of which have been much obscured by the nature of the terminology employed and by the neglect of that precise study of the morbid histology of the disease which I have already had occasion to deplore. It is doubtless in the knowledge of everyone here that the term "Hodgkin's disease" was first introduced into medical literature by Sir Samuel Wilks in a paper published in Guy's Hospital Reports in the year 1865 (vol. xi, p 56). He applied it to cases similar to those already described by Hodgkin some years previously in his well known paper entitled "On Some Morbid Appearances of the Absorbent Glands and Spleen."[13] The term, although a graceful and well-deserved tribute to the pathological acumen of Hodgkin, was, from a purely scientific point of view, an unfortunate one from the outset, for of the cases originally described by Hodgkin two at least were certainly not true examples of the disease now associated with his name Cases more or less resembling in their clinical and gross pathological aspects those first described by Hodgkin were afterwards published on the continent in the same year as that in which Wilks published his paper and a French observer, Bonfils, showed that such cases were not attended by any increase in the white cells of the blood.[14] This absence of any increase of white cells in the blood formed such a marked distinction between these cases and those of so-called "lymphatic" leukæmia that Cohnheim in the year 1865 sought to emphasise the distinction by introducing into pathology the unfortunate term "pseudo-leukæmia,"[15] whilst three years later we find Trousseau in his ninety-first clinical lecture applying the term "adénie" to cases characterised by progressive enlargement of glands without blood change to mark them off from tuberculous and other glandular enlargement, cases of which, as he states, Hodgkin had already given a good description. Billroth[16] still further complicated matters by introducing the word "lymphoma," meaning thereby what Cohnheim meant by pseudo-leukæmia, but opposing it to the term "lymphosarcoma" which was employed by Virchow[17] and which Billroth wished to discard altogether or to restrict only to cases of true sarcoma of glands. Meanwhile the term "Hodgkin's disease" had come into general use in English literature, whilst "pseudo-leukæmia" found perhaps the greatest degree of acceptance on the continent. As clinical investigation became more accurate, however, and as the number of recorded cases increased, it began to be believed that in all probability more than one variety of morbid process was being so described and it is interesting to find Virchow declaring so long ago as 1892 that he had always regarded the term "pseudo-leukæmia" as a "Mischmasch," whilst in recent German writings there is a strong tendency to discard its use altogether and to substitute for it "malignant lymphoma" (Pappenheim) or "lymphomatosis" (Türk).[18]

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[13] Transactions of the Royal Medical and Chirurgical Society, vol. xvii., p. 68, 1832.

[14] Société Médicale d'Observations de Paris, 1856 (reference from Einhorn's paper in New York Medical Record, July 12th, 1902).

[15] Ein Fall von Pseudo-Leukämie, Virchow's Archiv, 1865, Band xxxiii., p. 451.

[16] Gen. Surg., Path., and Therap., fourth edition, 1869.

[17] Die Krankhaften Geschwülste, Band ii., p. 729, Berlin, 1864

It is refeshing to turn from these shifting quicksands of a changing nomenclature to the firmer ground of pathology, and, assuming that there is a group of cases which are characterised clinically by progressive enlargement of the lymph glands and sometimes also of the spleen without any increase of white cells in the blood—call them provisionally Hodgkin's disease or what you will—to ask whether such cases are marked by any characteristic morbid histology. Curiously enough, this aspect of the question has been largely neglected. While many have put on record cases, called them by one or other of the above names and described in some instances their gross morbid appearances, few have undertaken to give any accurate description of the histological changes met with in the affected structures. This omission has, however, been fully repaired in recent years (though the descriptions do not yet seem to have found their way into the text-books) and that largely, one is glad to be able to say, by the labours of English and American workers. Even so far back as 1878 an extremely careful account of the histological characters of Hodgkin's disease was given by Professor Greenfield[19] in a paper read before the Pathological Society of London and published in its Transactions. He described the essential change as consisting in "a sort of chronic inflammation involving especially the fibrous stroma of the gland" and recognised the so-called soft and hard forms of the disease, the glands in the soft or early form being somewhat generally enlarged and the fibrous stroma appearing coarser than normal, whilst a large number of multinucleated cells containing from four to 12 nuclei could be observed adherent to the trabeculæ and often gathered into clusters where the fibrous change was progressing. In the more advanced—or what would be called by some the harder form—he found the glands practically converted into cicatricial tissue. He also described very carefully the characteristic histological changes in the spleen and the mode of their development. This description has been amplified but not in any important respect amended by the observations of subsequent workers. In a recent discussion at the Pathological Society on Lymphadenoma in its Relation to Tuberculosis[20] a very full description of the characteristic histology of Hodgkin's disease was given by Dr. F. W. Andrewes. He states that he has found the following changes: "1. The general plan of the structure of the gland is obscured and simplified; the distinction between cortex and medulla is abolished or nearly so, so that the whole gland has a more homogeneous appearance. 2 The number of lymphocytes is apparently very much decreased, they are proportionately scanty and no longer conceal the supporting framework of the gland. 3. In correspondence with this the framework has undergone hyperplasia, the fibrillar reticulum is conspicuous—its increase may amount to an actual fibrosis. The endothelial cells in connexion with it are more numerous and much more evident, here and there some of them attain a very large size and may contain two, four, or more large and deeply stained nuclei. These are the cells specially characteristic of lymphadenoma described by Virchow. ...... They may properly be described as lymphadenoma cells and though they are large multinucleate cells they have little resemblance to the giant cells met with in tubercle. They are not so large as the latter, they are more rounded and their nuclei, fewer in number, are larger. They stain more deeply and occupy a more central position; their protoplasm has less tendency to degenerative changes. 4. The eosinophile cells present in normal glands are always demonstrable in lymphadenoma, sometimes but not always, in vastly increased number."

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[18] Pseudo-leukämie und Lymphosarkomatose. Wiener Klinische Wochenschrift, 1899, No. 40; and Pappenheim (Ueber Pseudoleukämie und verschiedene verwandte Krankheitsformen), Archiv für Klinische Chirurgie, 1903, Band lxxi., p. 271.

[19] Specimens Illustrative of the Pathology of Lymphadenoma and Leucocythæmia, Transactions of the Pathological Society of London, 1877-78, vol. xxix., p. 272.

Miss Dorothy M Reed in a paper published in the Johns Hopkins Hospital Reports[21] has also dealt very fully with the minute anatomy of Hodgkin's disease. The microscopical changes, though apparently quite variable, always represent some stage in the same general process In the earliest stage one finds only proliferation of the flat, so-called endothelial cells which cover the reticulum of the lymph sinuses and of the large cells of the centres of the lymph nodes which are presumably identical with these. Mitotic figures in cells of t is description are frequently seen. Dilatation of the blood-vessels and the lymph sinuses is usually a marked feature of the early stage. As the process advances we find the lymph sinuses and the reticular spaces filled with masses of lymphocytes and proliferating endothelial cells. The presence of these newly formed cellular elements destroys the normal appearance of the gland by obliterating the distinction between the follicles and the sinuses. The endothelial cells, which show many karyokinetic figures, form in proliferating large epithelioid cells with vesicular nuclei. Numerous giant cells with one or more nuclei and prominent nucleoli appear in great number. These give evidence in their structure and situation of being derivatives from the epithelioid cells and in places they are the most prominent feature of the specimen. As the process advances the connective tissue shows marked proliferation. The framework of the gland becomes increased and bands of connective tissue, starting often from about the vessels, gradually break up the gland substance into coarse lobules. This process takes place at the expense of the other cells and the tissue undergoes a fibrous transformation which may increase until the coarse bands of fibrous tissue are more prominent than the small celluar islands which they include. Large areas which can only be explained as anæmic necroses are frequently observed, the centres of which show completely degenerated cells with fragmented nuclei, whilst the surrounding connective tissue often exhibits hyaline transformation. It is evident, as Miss Reed points out, that a gland examined at varying periods in the process would appear very different to casual observation. In the early stages we have a very cellular tissue in which the predominating element is the lymphocyte. This represents presumably the soft type of the disease and we can understand why Hodgkin's disease is usually spoken of as a simple hyperplasia of the lymph gland. The fibrosis of the later stage represents the "hard type" and the connexion between the two is not at first obvious. The process in its early stage has been frequently confused with sarcoma and in the later stage with tuberculosis. She agrees with Dr. Andrewes in considering that eosinophile cells are usually present in great number in Hodgkin's disease but not invariably.

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[20] Transactions of the Pathological Society of London 1902, vol. liii., p. 297.

[21] On the Pathological Changes in Hodgkin's Disease, with especial reference to its Relation to Tuberculosis, 1902, vol. x., p. 133.

Enough has been said, I hope, to show that cases such as that which I have described above are associated with definite histological changes in the affected structures and we have now to discuss the nature of the pathological process by which these changes are brought about. Two hypotheses have been advanced in this connexion, one that the process is a malignant one, allied to sarcoma formation, and the other that it is "infective" in origin. Of these the latter, or "infective," view has now won its way to almost universal adoption and it would be superfluous to enter here and now into the arguments which have been advanced in its favour. Of the nature of the infective agent, however, we are still in ignorance. A few years ago there arose a strong inclination to regard the tubercle bacillus as the infective agent, Askanazy being one of the first to point out that tuberculous lymphoma might run the clinical course of a febrile pseudo-leukæmia. This view was strongly espoused by Sternberg and elaborately advocated in a paper in which he described the clinical characters and microscopical changes in 15 cases.[22] His position was for a time widely adopted[23] but recently a reaction against it has been manifest for which the more accurate histological studies of Andrewes,[24] Reed,[25] and Simons[26] are largely responsible. It is now recognised that the mere presence of tubercle bacilli in the affected glands in Hodgkin's disease as demonstrated either microscopically or by inoculation experiments is no proof that they are the *cause* of the changes found in the glands, whilst those who have most accurately studied these changes are convinced that they are quite distinct from those characteristic of tuberculous processes. It would seem that the subjects of Hodgkin's disease are specially apt to become infected secondarily either by the tubercle bacillus or by other infective organisms which may gain access to the lymphatic circulation, a circumstance which is not surprising when one remembers how greatly the number of lymphocytes in the affected glands is reduced by the overgrowth of the stroma, whilst it is to the lymphocytes in all probability that the arrest of casual infections is in normal conditions to be attributed. It is to such secondary infections most likely that the variability in the clinical course of cases of Hodgkin's disease and the intermittent pyrexial attacks which they often exhibit are due, whilst at the same time they are usually the immediately determining cause of the fatal issue of the disease.

Hitherto, it must be admitted, all attempts to trace the presence of any one infective agent have been baffled. Various organisms, pyogenic and other, have been isolated from the glands by different observers, but the claims of none to be regarded as the cause of the disease are supported by any overwhelming mass of evidence. It is possible, of course, that Hodgkin's disease is not really a definite pathological entity but represents merely the reaction of adenoid tissue to any mild chronic irritant present in the circulation of which the tubercle bacillus, possibly in an attenuated form, is merely one. But this, I need hardly say, is not a position in which pathological investigation can be content to rest, and towards identifying the true nature of the infective agent, if such there be, the efforts of future investigators must be directed. Meanwhile the term "Hodgkin's disease" must remain a purely clinical one, comprehending a group of cases which present certain symptoms and signs in common irrespective of the exact pathogenic agent at work in any given case. In future, however, if clinical and pathological observations are to advance hand in hand in unravelling this group of cases and in subdividing it into smaller groups in accordance with their causation more attention than hitherto must be bestowed on some points of clinical investigation. In particular we need more accurate descriptions of the condition of the blood in future cases and more frequent recourse should be had to the tuberculin test.

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[22] Zeitschrift für Heilkunde, 1898, Band xix., p. 21.

[23] See papers by Schur (Wiener Klinische Wochenschrift, 1903, No. 5): Hutschmann and Stross (Deutsche Medicinische Wochenschrift, 1893, No. 21).

[24] Loc cit.

[25] Loc. cit.

[26] The Journal of Medical Research, New Series, vol. iv., June, 1903.

I have not so far discussed the question whether or not Hodgkin's disease is associated with any characteristic "blood picture." It has been customary to say that it is characterised by some degree of general anæmia—at all events in the later stages—but without any increase in the white cells. This, however, is not sufficient; we want more accurate information as to the relative proportions in which the different varieties of leucocytes are met with in cases of this group. In recent years a certain amount of attention has been devoted to this point and a considerable number of observations have accumulated but not yet sufficient to permit of any general statement being made. One set of writers, of whom Pinkus may be taken as the chief representative, maintain that Hodgkin's disease is characterised by a relative increase of the lymphocytes but others of equally high authority deny that this is the case, at all events invariably. Of seven cases described by Miss Reed[27] there was a relative and absolute increase of the small mononuclear leucocytes in two only, whilst in two other cases these cells were notably few in number; otherwise the blood counts were normal. And of ten undoubted cases (occurring at different ages) of which I have notes there was a polynuclear leucocytosis in two; in one both polynuclear and mononuclear forms were somewhat increased; in five the polynuclears were diminished—that is to say, the lymphocytosis was relative only; and in two alone was there a slight absolute lymphocytosis.

What we want to know is whether the occurrence of a polynuclear leucocytosis is only observed in those cases in which there has been a secondary infection, say with the tubercle bacillus. I am bound to confess that there was no sign of this, to ordinary naked-eye examination at least, in the two cases of my series in which the polynuclear cells were in excess but we want more information on the point. May such cases, perhaps, represent a special variety of the disease and be associated with a special infective agent? or does the relative numbers of the different cells present vary with the stage of the disease? Further, what is the relation of the blood picture to the size of the spleen? I have a general impression that there is a tendency for chronic enlargement of the spleen from any cause to be associated with a relative excess of lymphocytes in the blood, and if so is it only in those cases of Hodgkin's disease in which the spleen is markedly enlarged that such an occurrence is to be observed? To all of these questions no reply can be given until we are in possession of a sufficient number of cases which have been not only accurately observed during life but thoroughly examined after death. As regards the post-mortem examination of such cases I would urge the necessity of a microscopical examination of the bone marrow in every instance. In the whole literature of the subject there is, I regret to say, not a single paper with which I am acquainted which gives a description of the state of the histological changes in the bone marrow, if any, in this disease.

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[27] Op. cit.

The other way in which future clinical observation might be made of greater service to pathology would be, as I have said, by making more frequent use of the tuberculin test. I am aware that here also we are exposed to the danger of fallacious conclusions. A positive reaction to tuberculin does not necessarily show, any more than the finding of tubercle bacilli in the affected glands, that the process has been to start with a tuberculous one, nor does the absence of such a reaction conclusively negative the possibility of tuberculosis being present. I cannot help thinking, however, that if such tests were made earlier and oftener the results would prove to be of great value. The worth of such observations would be greatly increased if at the same time a gland was excised early in the course of the disease for careful microscopical examination and, if necessary, for inoculation experiments. The ease with which local anæsthesia can now be induced has rendered the trivial operation which this would necessitate practically devoid of inconvenience to the patient and I now make it a rule to employ it in every case where no objection is raised. Were such observations made in a sufficient number of cases and early in the course of the disease we should soon be in a position to say definitely whether or not Hodgkin's disease is ever really tuberculous from the outset. I feel convinced that it is on such lines as these that our observations must be conducted in future if the clinician is to take his proper share in helping to elucidate the difficult problems of glandular disease.

As regards any light which may be thrown upon the nature of Hodgkin's disease by its incidence in childhood there is only this to be observed, that its period of maximum frequency certainly does not coincide with that of tuberculosis. Hodgkin's disease is, it is true, essentially an affection of early life. Of 43 cases recorded by Mitchell Clarke[23] ten were below the age of 10 years and 33 were below 40 years, and of 17 cases which were admitted to the London Hospital within the last two years two were below the ago of 10 years and seven were below the age of 20 years. The disease, however, is certainly not one of infancy and whereas tuberculosis attains its maximum incidence in childhood about the second year, Hodgkin's disease is decidedly rare below the age of five years. I do not wish to attach undue importance to this point. We know too little of the factors which determine the age-incidence of disease to justify us in drawing any wide conclusions from such statistical observations alone, but at the same time any fact in the natural history of such an obscure affection as this is worthy of note. I have dealt rather fully with this matter and have gone, perhaps, somewhat beyond the legitimate scope of these lectures in thus discussing questions of general pathology, but it is only by taking a wide view of the problem that the best methods of solving it can be adequately presented.

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[23] Discussion on Lymphadenoma, British Medical Association Meeting, September, 1901.

LYMPHOSARCOMA.

The following case may be taken as a type of malignant disease affecting adenoid tissue.

The patient, a boy, aged nine years, had been in bad health since an attack of enteric fever six years before. On admission he appeared to be suffering from anæmia only. He was very pale and with the exception that the glands in the neck were palpable no other physical signs were to be discovered. The red cells were greatly reduced in number and stained badly, macrocytes and microcytes were present, and some pear-shaped forms, and a few normoblasts were discovered. The white cells numbered 5000 per cubic millimetre and the different varieties appeared to be present in normal relative proportions. At first the case was regarded as being possibly one of pernicious anæmia. A month later, however, periosteal growths appeared in the skull and in the neighbourhood of the orbits, so that one began to think of the possibility of chloroma. Blood films now showed a decided lymphocytosis; there were 57 per cent. of uninuclear and 43 per cent. of polynuclear forms in the films. From this time he went steadily downhill, the growths on the skull rapidly increased in size and number, and he died a few weeks later.

The following is a summary of the post-mortem report. The body was very pale and all the blood was fluid. The sternum was soft and infiltrated by a mass of growth which had removed its anterior bony wall so that the growth in front was covered by periosteum only. All the ribs were also invaded by masses of yellowish growth containing numerous points of hæmorrhage. The thoracic organs presented no important change. The retroperitoneal glands were involved in a mass of growth which enveloped the spinal column. The spleen, kidneys, suprarenals, pancreas, and liver appeared to be healthy. Adherent to the iliac vessels and to the nerves of the lumbar plexus was a mass of hard conglomerated growth which was breaking down at places into a greenish-yellow mass. On removing the scalp the skull was found to be studded with innumerable masses of very variable size, some being scarcely visible whilst others were as large as the end of the thumb. They varied in colour from pure white to a deep purple and resembled on section a lymphatic gland. The frontal sinus was bulged and filled with a mass of yellowish growth covered externally by periosteum only. This mass had invaded the roof of the orbit. The whole of the inner surface of the calvarium presented a worm-eaten appearance from growths which had penetrated the bone and the external surface of the dura was studded with similar growths. The base of the skull and the bones of the vertebral column were also infiltrated but the brain and cord were healthy. Microscopically the glands most affected were packed with small round cells, rather larger than ordinary lymphocytes, which had broken through the capsule and invaded the adjacent bone of the vertebral column. The ordinary gland structure was lost. The spleen pulp was stuffed with similar small round cells so that on section it resembled a gland, and similar collections of cells were found here and there between the tubules of the kidney. The lungs and liver exhibited no change.

Such a case as this presents many points of interest. In the first place, I think, it must be regarded as an example of the soft form of lymphosarcoma, meaning by that a growth which begins in adenoid tissue, invades locally, spreads by the lymphatics but not usually (? ever) by the blood, very rarely forms true metastases and does not exhibit any tendency to degenerative changes (Kundrat[29]). The starting point in this case appears to have been in the retroperitoneal glands and the question arises, Were the growths in the bone examples of true metastases or were they due to a similar sarcomatous process starting in the adenoid cells contained in the bone marrow? The case resembles in many respects those of multiple secondary carcinoma of bone described by Frese[30] and others, particularly in the marked anæmia by which it was accompanied and which was of so profound a degree as to suggest at first a diagnosis of pernicious anæmia. This no doubt was due to an extensive replacement of blood-forming tissue by new growth. The presence of a marked lymphocytosis is also of great interest. A similar occurrence was noted by Strauss[31] in a man, aged 72 years, whose case closely resembled that already described in that he exhibited multiple sarcomata of the bones and lymphatic glands and showed a leucocytosis of 57,600 per cubic millimetre, mainly mononuclear in type. The occurrence of some degree of lymphocytosis in cases of sarcoma seems to be not uncommon and would probably be found to occur more frequently if it were carefully looked for. Von Limbeck,[32] for instance, gives a table of cases of sarcoma in which such an occurrence has been observed, notably one of lymphosarcoma in which the white cells rose to 55,000 per cubic millimetre. The increase, he says, "is not wholly one due to the polynuclears but partly also to the mononuclears." It is in cases in which the bones are extensively involved, however, and in which the cells of the growth have direct access to the blood that one would most expect to meet with a lymphocytosis and such cases, if any, merit the designation "sarcomatosis of the blood." Mere periosteal growths, however extensive, do not appear to produce this effect. I have seen, for instance, three remarkable cases of sarcoma in the neighbourhood of the suprarenal in young children attended by extensive periosteal growths in the skull which clinically closely resembled the case described above. Yet in none of these was there any increase in the lymphocytes of the blood and after death the bones were found not to have been invaded. The diagnostic value of lymphocytosis will be referred to immediately.

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[29] Ueber Lymphosarkomatosis, Wiener Klinische Wochenschrift, 1893, Nos. 12 and 13.

[30] Deutsches Archiv für Klinische Medicin, 1900, Band lxviii., p. 387.

[31] Sarcomatose und Lymphatische Leukämie, Charité Annalen, 1898, Band xxiii., p. 383.

[32] Pathologie des Blutes (New Sydenham Society's Transactions, p. 236).

RELATIONS OF THESE PROCESSES.

I have described multiple tuberculous adenitis, Hodgkin's disease, and lymphosarcoma as types of three pathological processes affecting adenoid tissue in a primary and widespread fashion and the further question now arises are these entirely distinct or do intermediate or mixed pathological types occur? As regards the question of tuberculous adenitis and Hodgkin's disease I have already expressed the opinion that these are entirely distinct and separate and that each of them is characterised by its own peculiar morbid histology. It has also been indicated, however, that glands which have been primarily affected by Hodgkin's disease may become secondarily the seat of tuberculosis and that it is to such secondary or terminal infections that much of the confusion which has hitherto prevailed regarding the identity of Hodgkin's disease is to be attributed. It was also pointed out when discussing the nature of the latter disease that it was possible that it might sometimes be produced by a peculiar and possibly attenuated tuberculous infection, though of this no convincing proof has yet been brought forward. On the other hand, between Hodgkin's disease and lymphosarcoma there is, I believe, no relationship. The morbid histology of the former is quite distinct from that of even the more fibrous forms of lymphosarcoma such as are met with in the mediastinum. Lymphosarcoma is often, though not always, attended by an absolute lymphocytosis which may reach quite a high degree, whereas the lymphocytosis of Hodgkin's disease, though also inconstant, is at best merely relative and due not so much to an absolute increase of lymphocytes as to an absolute reduction in the number of the polynuclear forms. To class Hodgkin's disease and lymphosarcoma together under the title of "lymphomatosis," as some German writers propose to do,[33] seems to me, therefore, reactionary and calculated to retard our real knowledge of each disease and is to be attributed mainly to a failure to recognise the characteristic morbid histology of Hodgkin's disease which has been established by the labours of English and American workers.

When we turn to consider a possible relationship between the diseases just described and the leukæmias dealt with in the last lecture we are on more uncertain ground. In discussing the use of the term "pseudo-leukæmia" as a substitute for "Hodgkin's disease" I had occasion to point out what confusion it had caused. This confusion is largely due to the fact that such a term as pseudoleukæmia suggests a relationship of Hodgkin's disease to leukæmia which has no foundation in fact. In this connexion much misapprehension has been brought about, in my judgment, by the exaggerated importance ascribed by some writers, notably by Pinkus, to the supposed lymphocytosis of Hodgkin's disease. Now lymphocytosis, whether absolute or relative, is, as we have seen, by no means a constant phenomenon in Hodgkin's disease. That cases of true lymphatic leukæmia do occur in which, at one stage of the process at least, there is no *absolute* increase of the total leucocytes must be admitted but in such cases there is notwithstanding a marked absolute increase of lymphocytes, whilst the normal total count is due to a great reduction of the polynuclear forms. The supposed analogy between the blood pictures of the two diseases is therefore fallacious. In addition to this the morbid histology of the two processes is totally distinct, lymphatic leukæmia being a disease which affects only the parenchyma of the glands and adenoid tissue generally, whereas in Hodgkin's disease it is the supporting tissue which is mainly involved. Further, I have met with no case in my own experience either in the child (in whom, as we have seen, lymphatic leukæmia is relatively rather frequent) or in the adult, in which leukæmia appeared to pass into Hodgkin's disease or *vice versâ*, nor have I found any record of such a case in my reading. I think we may safely conclude, therefore, that between Hodgkin's disease and leukæmia there is no relation and that the two diseases belong to totally different orders of pathological processes. I may appear, perhaps, to have laboured this conclusion overmuch, for I doubt not that in this country at least few would be found to demur to it, but one feels bound to protest against the attempts which are being made on the continent to bring so-called pseudo-leukæmia and lymphatic leukæmia together and to look upon them as differing in degree only and not also in kind

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[33] See Türk, Pseudoleukämie und Lymphosarkomatose, Wiener Klinische Wochenschrift, 1899, No. 4.

Between lymphatic leukæmia and lymphosarcoma, on the other hand, the possibility of a certain relationship is not so easily to be dismissed. Lymphosarcoma certainly possesses several points of resemblance to the more chronic forms of lymphatic leukæmia. In both we have to do with an overgrowth of the parenchymatous elements of the adenoid tissue, the difference being that in one case (leukæmia) the overgrowth is restricted to the organ primarily involved, whereas in the other (lymphosarcoma) it breaks through into surrounding tissues. The blood picture of the two diseases may also present very similar features. In both there is a profound general anæmia with an absolute increase of lymphocytes which is constant and of high degree in leukæmia, less constant but often very marked in lymphosarcoma. It is probable, however, that the lymphocytosis never reaches the same degree in lymphosarcoma as it does in typical lymphatic leukæmia unless, or indeed even when, the sarcomatous process has started in, and extensively involves, the bone marrow, though on this point we want further information, whilst the locally invasive character of lymphosarcoma marks it off quite definitely from any true lymphatic leukæmia.

One finds a connecting link between the two processes, however, in the disease termed "chloroma." This we may define with Günbel[34] as consisting of multiple green lymphomata localised chiefly in the periosteum and neighbourhood of the bones, especially of the head, and the loose connective tissue along the spinal column, accompanied by hyperplasia of the whole lymphatic apparatus, by lymphoid transformation of the bone marrow, and by a blood picture similar to that of lymphatic leukæmia. In its seat of election this disease presents a close resemblance to such a case of lymphosarcoma as that described above, though with less tendency to local invasion, for the lymphomatous growths of chloroma tend merely to "soak," as it were, along the lines of least resistance, such as the subcutaneous and subperiosteal tissues, rather than actively to invade neighbouring organs, whilst in its affection of the marrow and in the blood picture of which that is merely the reflection it presents a closer resemblance to lymphatic leukæmia. The latter resemblance is rendered still more close by the fact that cases of apparently pure lymphatic leukæmia are occasionally met with in which the enlarged glands exhibit the greenish colour usually regarded as characteristic of chloroma. Of this a well-marked example recently occurred in the London Hospital and others have been recorded by Byrom Bramwell[35] and Lindsay Steven.[36] We have thus, it would seem, in lymphosarcoma, in chloroma, and in lymphatic leukæmia three closely allied processes exhibiting a descending scale of malignancy but presenting many features in common and in the case of chloroma and lymphatic leukæmia at all events possibly tending to pass into each other. Of these lymphatic leukæmia is often met with in infancy, chloroma is more characteristic of childhood and adolescence, whilst lymphosarcoma tends to occur rather in the later periods of life.

I have now passed in review the most outstanding of the disorders which affect the blood and blood-forming organs in early life and it may be well for us to cast a glance back over the ground which we have traversed and to survey it for a moment as a whole. It will have been observed that the blood disorders of early life differ from those of more mature years mainly in exhibiting less definition of type. Such comparatively clear-cut disorders as pernicious anæmia, chlorosis, and myelogenous leukæmia—disorders, in a word, of the bone marrow—occur rarely, if at all, in infancy and early childhood, whilst several secondary anæmias and infective leukæmic and sarcomatous processes affecting

[34] Ueber das Chlorom und seine Beziehungen zur Leukämie, Virchow's Archiv, 1903, Band 171, p. 504.

[35] Notes of a Case of Chloroma and of Three Cases of Lymphatic Leukæmia, Scottish Medical and Surgical Journal, March, 1902.

[36] Glasgow Medical Journal, July, 1903.

adenoid tissue are relatively common. Peculiar to infancy is one type of anæmia only—namely, that which I have spoken of as anæmia splenica infantum, a variety which is in close relationship in its slighter degrees to the secondary anæmias, whilst in its severer manifestations it approximates to the type of the leukæmias. This affection, indeed, epitomises in itself all the peculiarities of the anæmias of infancy, exhibiting on the one hand the marked destruction of red cells with the ready appearance of nucleated forms which characterises the severer secondary anæmias of this age, whilst on the other it shows by the tendency for the non-granular cells in the blood to be increased that reaction of the adenoid tissue to unfavourable influences which is a striking peculiarity of childhood. The ease with which secondary anæmia develops in early life we have seen to be due in part to great vulnerability of the blood cells and in part to the poverty in hæmoglobin which seems to be natural to this period of life, whilst the special character of that anæmia—namely, the readiness with which normoblasts appear in the blood stream—may perhaps be ascribed to the restricted area of the red-cell forming tissue possessed by the infant. It must be remembered, also, that to many influences specially destructive of blood or inimical to its formation the period of infancy is peculiarly exposed. Amongst such influences are defective diet—in particular a diet deficient in proteids and in iron—chronic gastro-intestinal disorders, the syphilitic cachexia, and various infective processes with their resulting poisons. The tendency for the adenoid tissue to react in all the severe anæmias in infancy, with the consequent appearance of an excess of leucocytes in the blood stream, I have tried to correlate with the extensive development of that tissue in the first two or three years of life and with the active functions which it appears to discharge. The nature of these functions were briefly discussed, it will be remembered, and the suggestion was made that the activity of the adenoid tissue may be related to the processes of nutrition and growth. This very activity and extent of the adenoid tissue, moreover, seem to render it specially obnoxious to infective, leukæmic and malignant processes, whence the frequency of Hodgkin's disease, lymphatic leukæmia, chloroma, and lymphosarcoma in the earlier years.

At various points throughout these lectures I have had occasion to comment upon the absence of sharp differentiation between the different types of anæmia in early life. It was shown that the splenic anæmia of infancy tends to fade off at the lower end of the scale into the severer forms of secondary anæmia and at the upper into the leukæmias. It was pointed out, too, that forms of anæmia occur in early life which partake of the characters both of the lymphatic and of the myelogenous type, whilst between lymphatic leukæmia, chloroma, and lymphosarcoma fixed boundaries can hardly be drawn. This indefiniteness of type, it has been suggested, may be merely the reflection of an equal want of definition in the function of the various blood-forming organs in early life and of an incomplete division of labour amongst them. At all events, it may well be that, even although the differentiation of function on the part of the blood-forming organs in infancy is fairly complete in health, yet under adverse conditions a reversion may take place more easily than in the adult to the primitive conditions which obtain in the fœtus. In these circumstances the territorial distinctions tend to be lost, the mother-cells of the bone marrow (myelogonia) no longer producing merely myelocytes and those of the adenoid tissue (lymphogonia) lymphocytes, but both myelogonia and lymphogonia combining to produce that species of cell the demand for which in the blood stream is greatest at the moment. It is in this direction, I believe, that further study of the blood disorders of early life is likely to lead to results which will materially modify our conceptions as to the processes of blood formation in general.

In conclusion, I would say that no one here can feel more acutely than myself the many shortcomings of these lectures and how unworthy they are of this audience and this place. I have tried to deal with a subject of great difficulty and often of great obscurity and in looking back I fear that I have been able to illuminate it but little I shall not have wholly failed, however, if I have succeeded in bringing into clearer prominence the peculiar nature of the problems presented by a study of the blood disorders of early life and in suggesting lines of fruitful work for future investigators. In any case I can only hope that the kindness which called me to this position, for which I wish to return my sincere thanks, will be equal also to the task of overlooking the poverty of my efforts to fulfil its obligations.

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